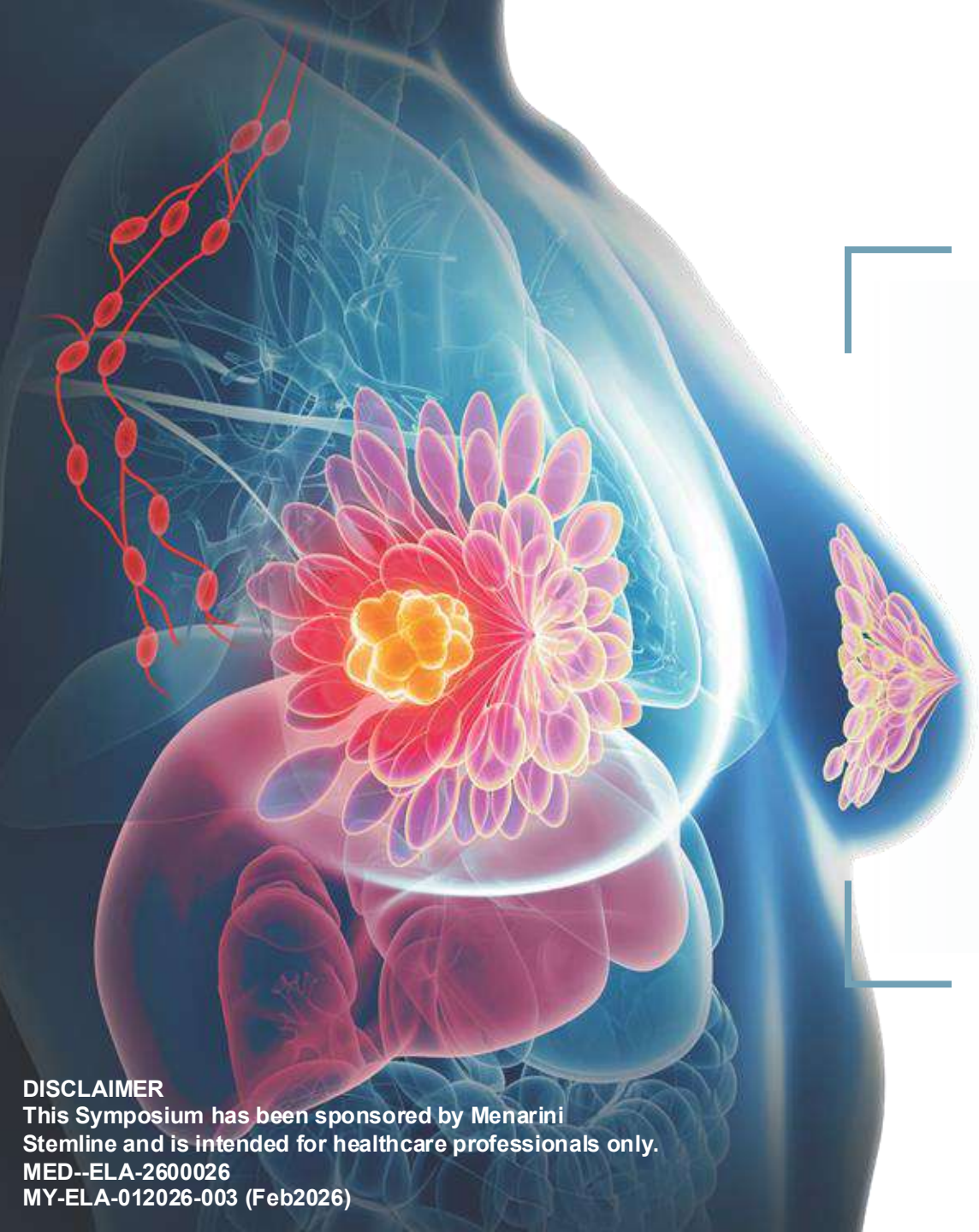

Strategic Treatment Sequencing and Novel Approaches in

2L+ ER+/HER2– mBC

Sunday, February 8, 2026

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Faculty

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worked with NGOs championing cancer awareness, early diagnosis and treatment.

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Disclosures

Faculty disclosures

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Non-financial interests: Member of the executive board of the BIG; Board member of the ISFP; ASCO Annual Meeting Scientific Program Committee on the Breast Cancer – Local/Regional/ Adjuvant Track

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Agenda

Time	Title	Presenter
10 min	Welcome and introduction, Evolving standards in 2L+ ER+/HER2– mBC	**Mastura Md Yusof**
25 min	Treating endocrine therapy-eligible patients after 1L progression	**Hope Rugo**
15 min	Biomarker driven treatment decisions: Evolution of *ESR1* testing	**Matteo Lambertini**
10 min	Discussion and Q&A	**All**

1/2L, first/second line; CDK4/6, cyclin dependent kinase 4/6; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

Housekeeping

Please keep your cell phone on silent mode and refrain from using other electronic devices during the presentation.

Microphones will be provided for live audience questions at the end of the session.

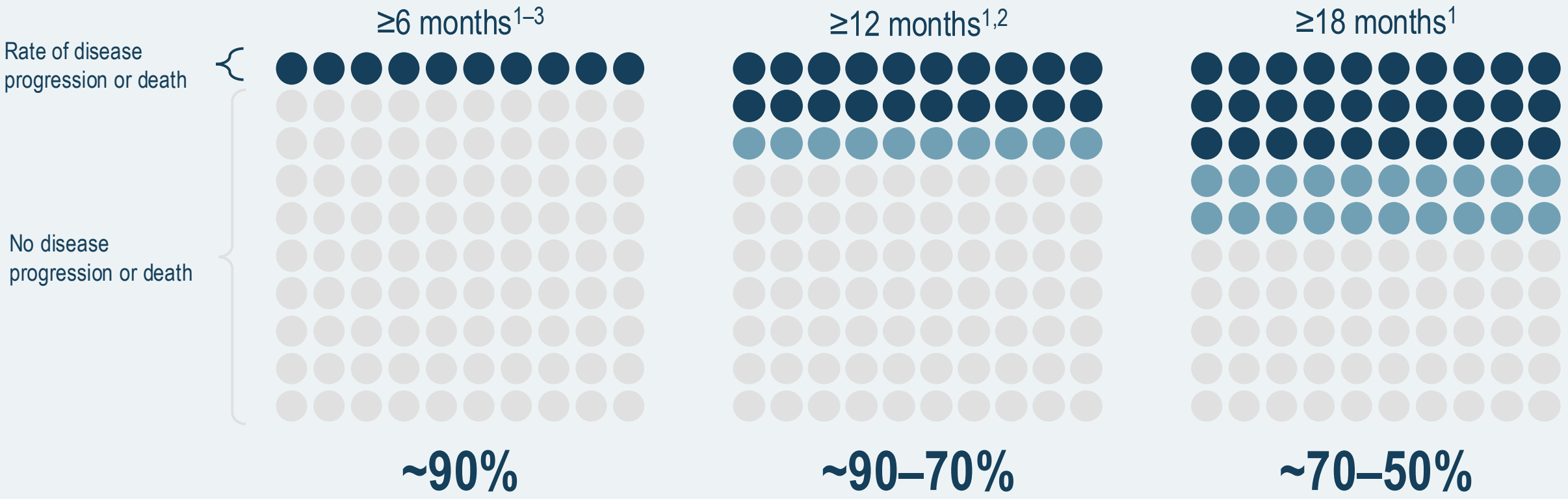
Evolving Standards in 2L+ ER+/HER2– mBC

Mastura Md Yusof

PICASO Cancer Centre, Hospital PICASO, Petaling Jaya, Malaysia

2L, second line; ER, estrogen receptor; HER2, human epidermal growth factor 2; mBC, metastatic breast cancer.

Real-world data show that the vast majority of patients are exposed to 1L CDK4/6i + ET for ≥12 months[1–3]



1L, first line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy.

1. De Laurentis M, et al. SABCS 2019. Poster P3-11-25; 2. Suzuki DA, et al. *JCO Glob Oncol.* 2024;10:e2300484; 3. Nozawa K, et al. *Breast Cancer.* 2023; 30:657–665.

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Eligibility for endocrine therapy can be classified by clinical variables[1–4]

Primary endocrine resistance

PD within first 6 months of 1L ET-based therapy for advanced breast cancer, while on ET (regardless of CDK4/6i use)[1]

Usually non-eligible for ET regimens

Secondary endocrine resistance

PD after ≥6 months of 1L ET[1]
or
PD after any duration of 2L+ ET-based therapy[1]

Eligible for ET regimens

1L, first line; 2L+, second line and beyond; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; PD, progressive disease.

1. Cardoso F, et al. *Breast*. 2024;76:103756; 2. Rani A, et al. *Front Endocrinol (Lausanne)*. 2019;10:245; 3. Gennari A, et al. *Ann Oncol*. 2021;32(12):1475–1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.2 April 2025 (Accessed July 2025); 4. Trapani D, et al. *Ann Oncol*. Published online August 12, 2025.

Treatment for patients eligible for 2L endocrine therapy is defined according to the presence of genomic alterations

Intrinsic alterations

Includes alterations of the PI3K/AKT/mTOR pathway, *BRCA1/2* mutations, *RB1* loss, *TP53* alteration[1,2]

Acquired mutations

Mechanisms of resistance, such as *ESR1* mutations, may occur up to 50% of patients after prior endocrine therapy in mBC[3-5]

2L, second line; AKT, protein kinase B; *BRCA1/2*, BReast CAncer gene 1/2; *ESR1*, estrogen receptor 1 gene; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; RB1, retinoblastoma 1; TP53, tumor protein p53.

1. Rani A, et al. *Front Endocrinol (Lausanne).* 2019;10:245; 2. Xu XQ, et al. *Acta Pharmacol Sin.* 2021;42(2):171–178; 3. Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85; 4. Jhaveri KL, et al. J Clin Oncol . 2024.10;42(35):4173-4186; 5. Bhave MA, et al. *Breast Cancer Res Treat*. 2024;;207(3):599-609.

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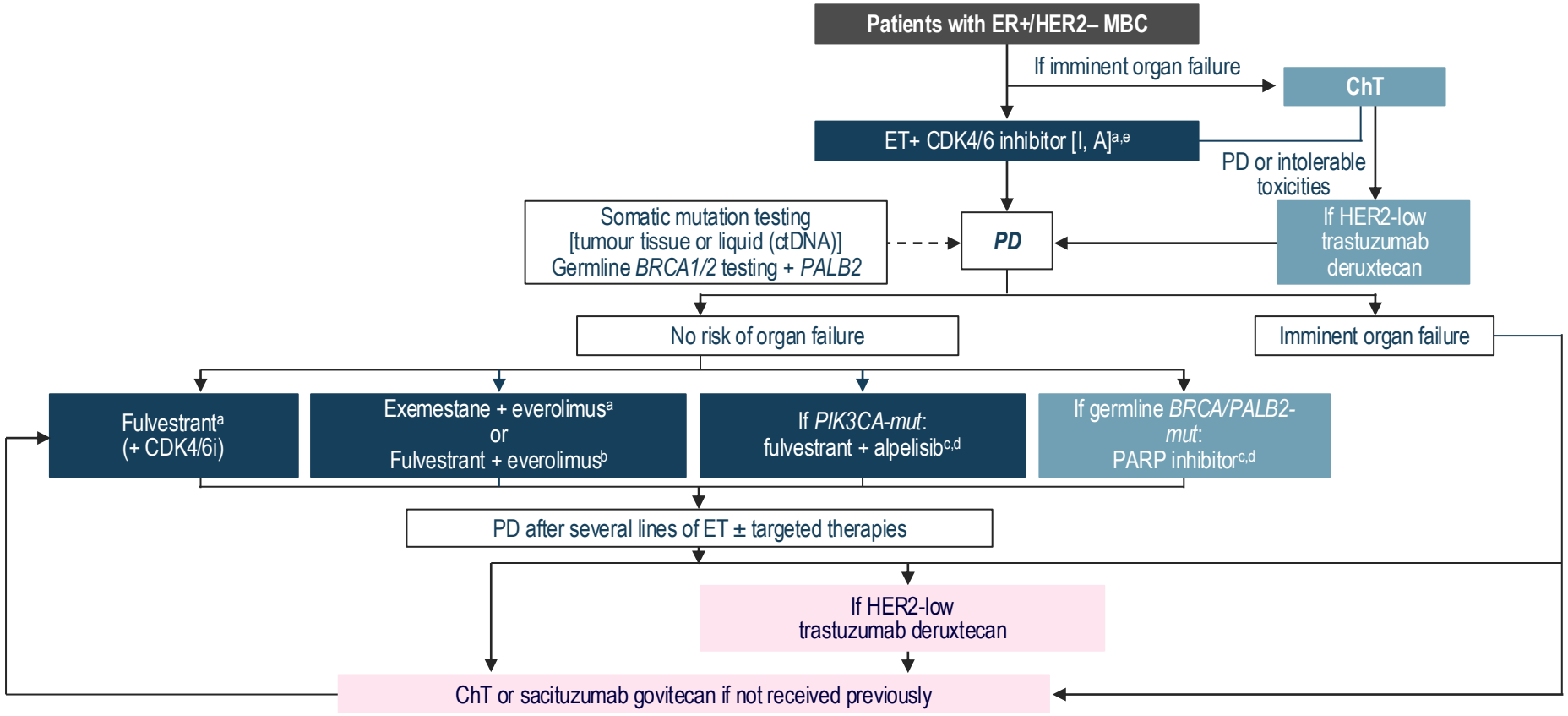
Pan-Asian ESMO Clinical Practice Guidelines recommend exhausting sequential ET-based regimens in 2L+ setting[1]



Grey box: general categories or stratification; dark blue boxes: combination of treatments or other systemic treatments; white boxes: other aspects of management; light blue boxes: systemic anticancer therapy; pink: trastuzumab deruxtecan in HER2low.

[a]OFS if the patient is premenopausal; [b]Preferred if the patient is *ESR1* mutation positive [ESCAT score: II-A]; [c]ESMO-MCBS v1.1[3,4] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; ChT, chemotherapy; ctDNA, circulating tumour DNA; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESR1, estrogen receptor 1; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; m, mutation; MBC, metastatic breast cancer; MCBS, ESMO-Magnitude of Clinical Benefit Scale; OFS, ovarian function suppression; PALB2, partner and localiser of BRCA2; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. S-A Im, et al. ESMO Open. 2023 Jun;8(3):101541.

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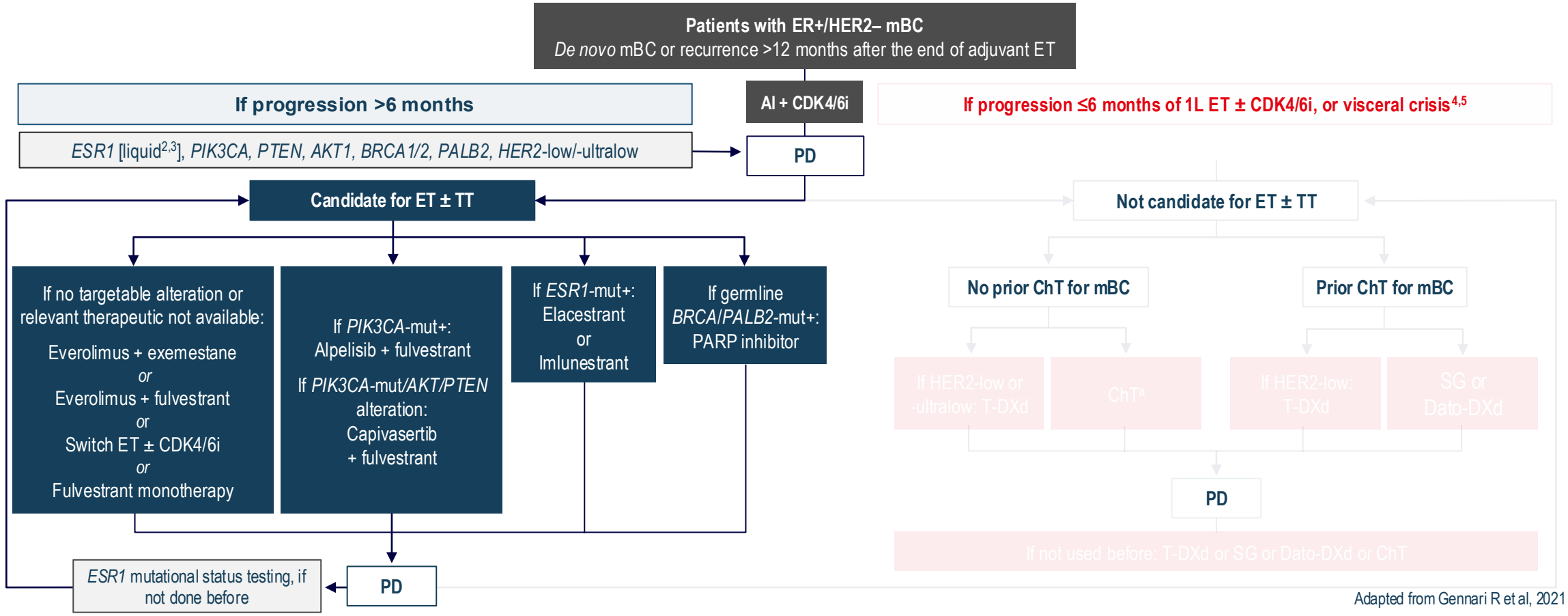
Treating Endocrine Therapy-Eligible Patients After 1L Progression

Hope Rugo

City of Hope Comprehensive Cancer Center, United States

ESMO Guidelines recommend assessing clinical eligibility and mutational status testing before initiating an endocrine therapy-based treatment[1]



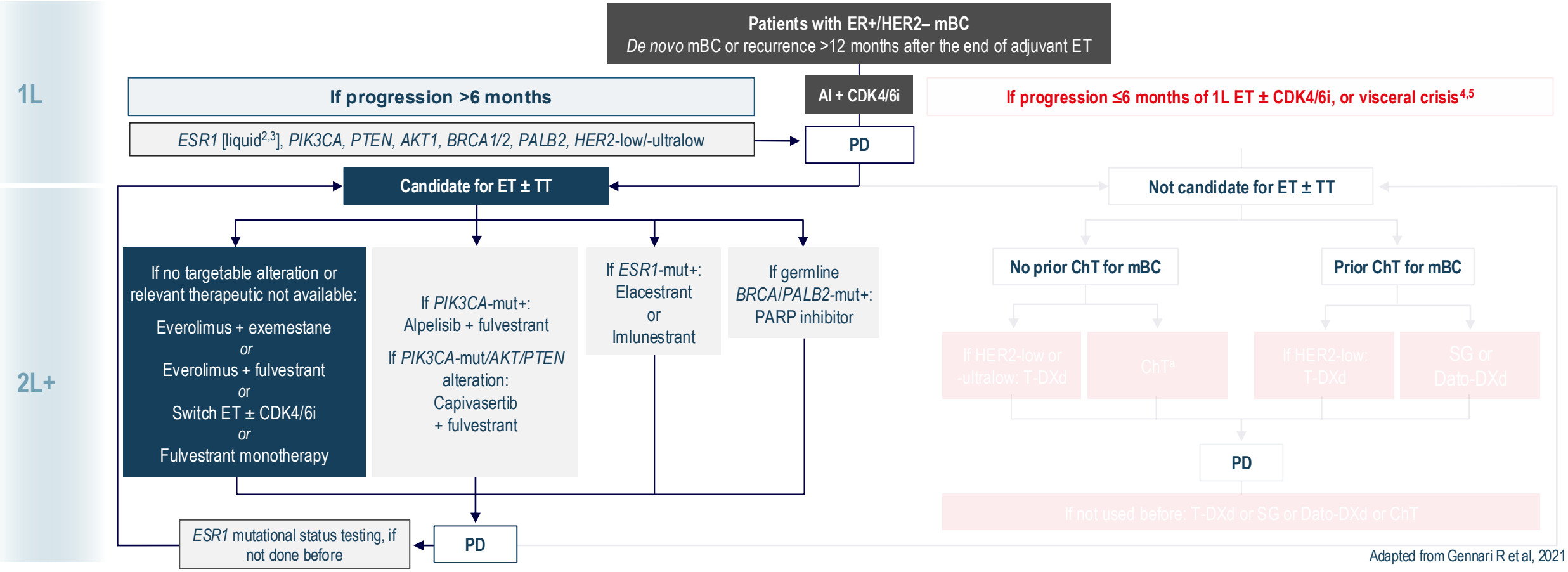
Adapted from Gennari R et al, 2021

[a]Taxane–bevacizumab or capecitabine–bevacizumab. 1L, first line; 2L+, second line and beyond; AI, aromatase inhibitor; AKT1, protein kinase B alpha; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ChT, chemotherapy; Dato-DXd, datopotamab deruxtecan; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mut+, mutation positive; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and TENsin homolog; SG, sacituzumab govitecan; SOC, standard of care; T-DXd, trastuzumab deruxtecan; TT, targeted therapy.

1. Adapted from: Gennari A, et al. *Ann Oncol*. 2021;32(12):1475–1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.2 April 2025 (Accessed July 2025); 2. Burstein HJ, et al. *J Clin Oncol*. 2023;41(18):3423–3425;

4. Bardia A, et al. *N Engl J Med*. 2024;391(22):2110–2122; 5. Cardoso F, et al. *Breast*. 2024;76:103756.

Second-line treatment choice is defined by the eligibility to receive endocrine therapy and driven by biomarker status



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1. Adapted from: Gennari A, et al. *Ann Oncol*. 2021;32(12):1475–1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.2 April 2025 (Accessed July 2025); 2. Burstein HJ, et al. *J Clin Oncol*. 2023;41(18):3423–3425;

4. Bardia A, et al. *N Engl J Med*. 2024;391(22):2110–2122; 5. Cardoso F, et al. *Breast*. 2024;76:103756.

CDK4/6i rechallenge so far had mixed results in all-comers and negative results in *ESR1*-mut subgroup

	MAINTAIN[1,5]	PACE[2,5]	PALMIRA[3,4,6]	postMONARCH[5,6]
Phase (n)	Ph2 (119)	Ph2 (220)	Ph2 (198)	Ph3 (368)
Experimental arm	Ribociclib + fulv or exemestane	Palbociclib + fulv[a]	Palbociclib + fulv or letrozole	Abemaciclib + fulv
Control arm	Fulv or exemestane	Fulv	Fulv or letrozole	Fulv (+ PBO)
***ESR1*-mut (%)**	30%	50%	N/A	40%
mPFS all patients mPFS, months HR (95% CI)	5.3 vs 2.8 HR 0.57 (95% CI 0.39–0.85)	4.6 vs 4.8 HR 1.11 (90% CI 0.74–1.66)	4.9 vs 3.6 HR 0.84 (95% CI 0.66–1.07)	6.0 vs 5.3 HR 0.73 (95% CI 0.57–0.95)
mPFS *ESR1*-mut mPFS, months HR (95% CI)	3.0 vs 3.0 HR 1.22 (95% CI 0.59–2.49)	5.2 vs 3.3 HR 0.68 (90% CI 0.42–1.09)	Not reported	Not reported HR 0.79 (95% CI 0.54–1.15)

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

[a]Palbociclib + fulvestrant + avelumab arm not considered for this table

2L, second line; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; ESR1, estrogen receptor 1 gene; ET, endocrine therapy; fulv, fulvestrant; HR, hazard ratio; (m)PFS, (median) progression-free survival; mut, mutation; NS, not significant; PBO, placebo; PFS, progression-free survival; N/A not available.

1. Kalinsky K, et al. *J Clin Oncol*. 2023;41:4004–4013; 2. Mayer EL, et al. *J Clin Oncol*. 2024.JCO2301940; 3. Llombart-Cussac A, et al. J Clin Oncol. 2025 Apr 28;43(18):2084–2093; 4. PALMIRA. ClinicalTrials.gov identifier: NCT03809988. Accessed August 2024, https://clinicaltrials.gov/study/NCT03809988; 5. Kalinsky K, et al. J Clin Oncol . 2025 Mar 20;43(9):1101-1112. 6. Bardia, et al. *Clin Cancer Res*. 2024; Online ahead of print.

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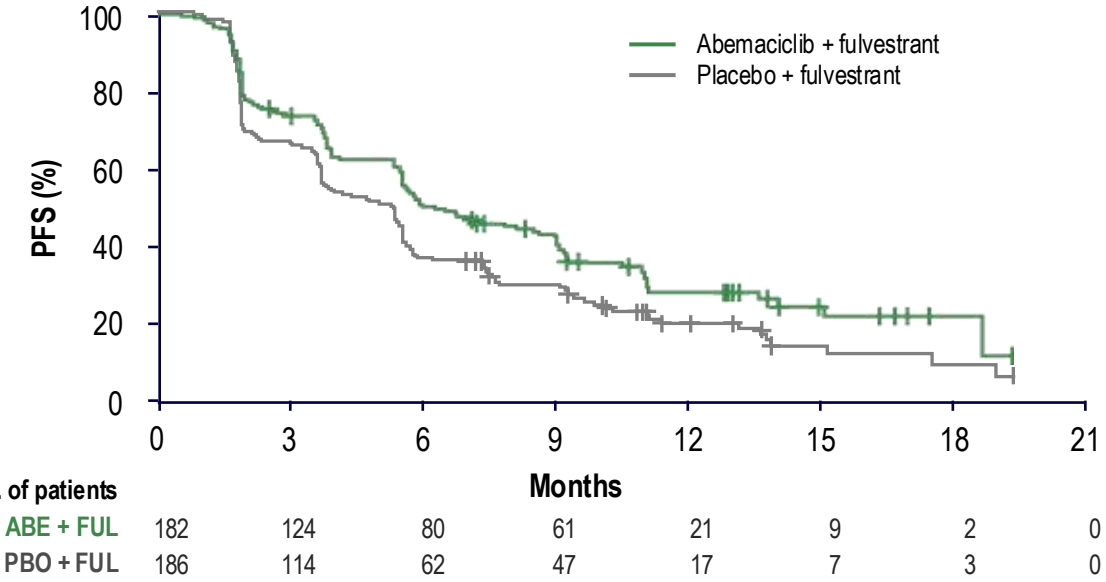
postMONARCH phase 3 trial: CDK4/6i rechallenge shows mPFS benefit mainly after palbociclib, with no benefit after ribociclib and in *ESR1*-mut tumors[1]

postMONARCH: ITT mPFS[a]



	ABE + FUL (N=182)	PBO + FUL (N=186)
mPFS, mo [95% CI]	6.0 [5.6–8.6]	5.3 [3.7–5.6]
HR [95% CI]	0.73 [0.57–0.95]	
Nominal p-value	0.02	

postMONARCH: Subgroup analysis

Subgroup	N (%)	events	HR (95% CI)	Interaction p-value
Visceral Metastasis				0.07
Yes	221 (60)	173	0.87 (0.64–1.17)	
No	147 (40)	85	0.53 (0.34–0.83)	
Liver Metastasis				0.40
Yes	139 (38)	115	0.63 (0.44–0.91)	
No	229 (62)	143	0.78 (0.56–1.09)	
Prior CDK4/6 inhibitor				0.19
Palbociclib	217 (59)	145	0.62 (0.44–0.86)	
Ribociclib	122 (33)	94	1.01 (0.67–1.51)	
Abemaciclib	28 (8)	19	0.66 (0.27–1.84)	
***ESR1*-mut**				0.98
Detected	145 (45)	110	0.79 (0.54–1.15)	
Not detected	175 (55)	120	0.79 (0.55–1.13)	

Biomarker ctDNA by GuardantINFINITY assay.
[a]Investigator-assessed PFS.
ABE, abemaciclib; CI, confidence interval; ctDNA, circulating tumor DNA test; DNA, deoxyribonucleic acid; FUL, fulvestrant; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

1. Kalinsky K, et al. J Clin Oncol . 2025 Mar 20;43(9):1101-1112.

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What about everolimus (mTORi) plus ET?

	BOLERO[1-3]	RWD Rozenblit et al.[4]	RWD Vasseur et al.[5]	TRINITI-1[6]	RWD EVERGREEN[7]
Phase (n)	Ph3 (724)	N/A (246)	N/A (57)	Ph1/2 (95)	N/A (207)
Experimental arm	Everolimus + exemestane	Everolimus + ET	Everolimus + fulvestrant	Everolimus + exemestane + ribociclib	ET + everolimus
Control arm	Placebo + exemestane	N/A	N/A	N/A	ET
Previous CDK4/6i	–	22%	100%	100%	100%
***ESR1*-mut, %**	30%	N/A	N/A	34%	N/A
mPFS all patients mPFS, months HR (95% CI)	**7.8 vs 3.2** 0.45 (0.38-0.54)	mTTNT Prior CDK4/6i: **4.3** No prior CDK4/6i: **6.2**	**6.8**	**5.7**	**5.0**
mPFS *ESR1*-mut mPFS, months HR (95% CI)	**5.4 vs 2.8** 0.52 (0.36-0.75)	**N/A**	**N/A**	**3.5**[a] N/A (1.9-7.3)	**N/A**

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

[a]N=89 patients had a baseline ctDNA biomarker assessment.

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ctDNA, circulating tumor DNA; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; eve, everolimus; HR, hazard ratio; mPFS, median progression-free survival; mTOR, mammalian target of rapamycin; mTTNT, median time to next therapy; mut, mutation; N/A not available; RWD, real-world data; rwPFS, real-world PFS; SOC, standard of care.

1.Yardley DA, et al. *Adv Ther*. 2013;30:870–884; 2. Cook M, et al. *Oncologist*. 2021;26:101–106; 3. Chandarlapaty S, et al. *JAMA Oncol*. 2016;2:1310-1315; 4. Rozenblit M, et al. *Breast Cancer Res*. 2021;23(1):14; 5. Vasseur A, et al. *Oncogene*. 2024;43(16):1214–1222 (including suppl); 6. Bardia A, et al. *Clin Cancer Res*. 2021;27(15):4177–4185; 7. Lobo-Martins SL, et al. *Ann Oncol*. 2024;35(suppl 2):S365–S366.

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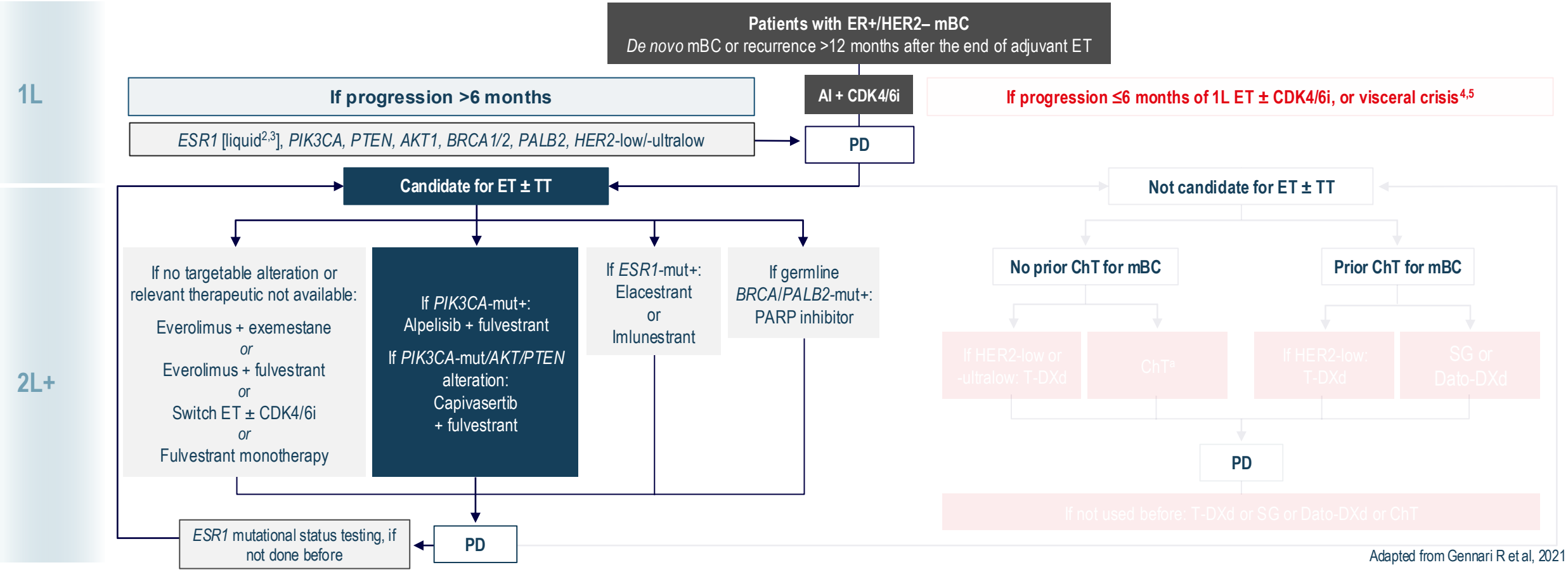
Second-line treatment choice is defined by the eligibility to receive endocrine therapy and driven by biomarker status



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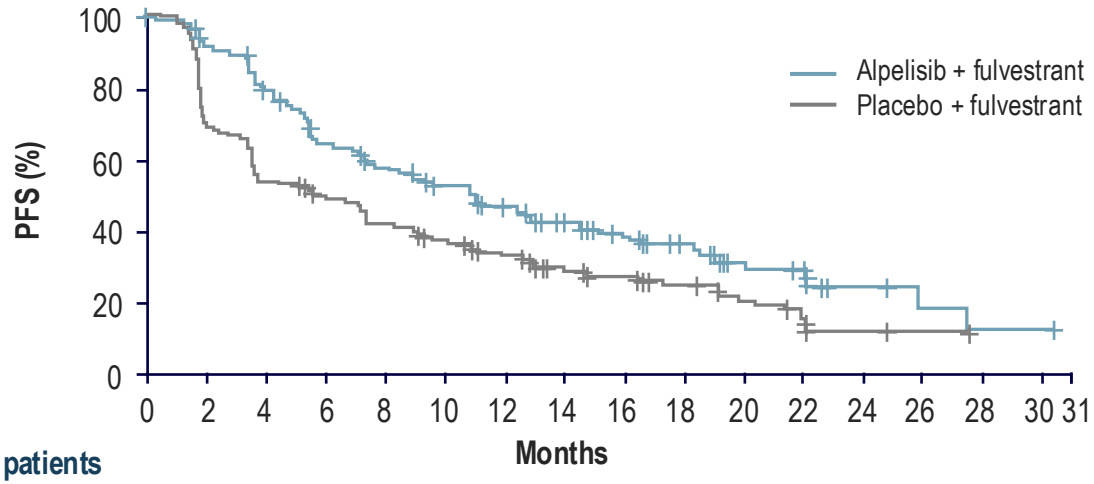
Alpelisib + fulvestrant in patients with ER+/HER2– and *PIK3CA*-mut mBC

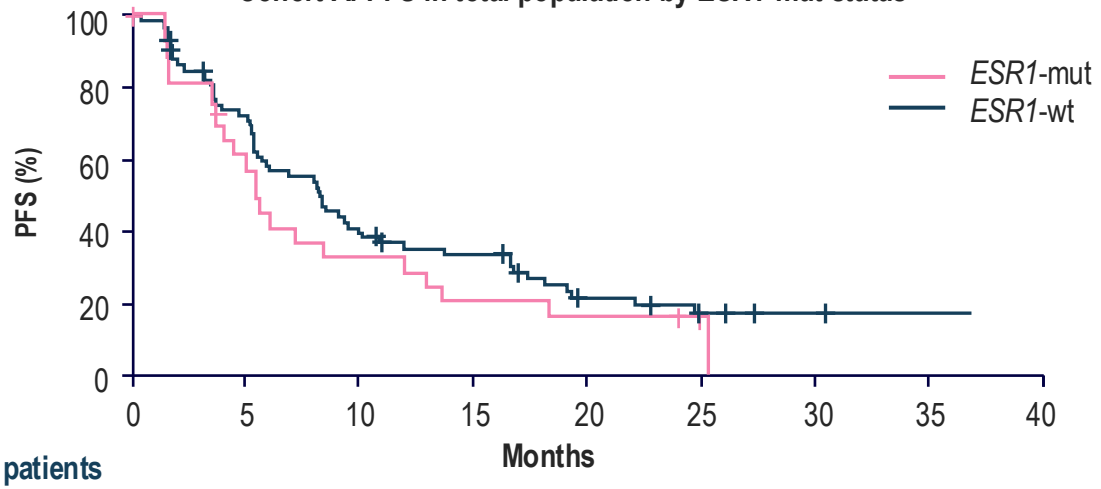
SOLAR-1: *PIK3CA*-mut[1]
Patients WITHOUT prior CDK4/6i therapy[a]



No. of patients																
ALPE + FUL	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0
PBO + FUL	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

	ALPE + FUL (n=169)	PBO + FUL (n=172)
mPFS, mo [95% CI]	**11** [7.5–14.5]	**5.7** [3.7–7.4]
HR [95% CI]	**0.65** [0.50-0.85]	
Log-rank p-value	<0.001	

BYLieve[2,3]
Patients WITH prior CDK4/6i therapy
Cohort A: PFS in total population by *ESR1*-mut status[2,3]



No. of patients									
ESR1-mut	27	15	8	5	4	1	0	0	0
ESR1-wt	75	51	28	21	11	4	2	1	1

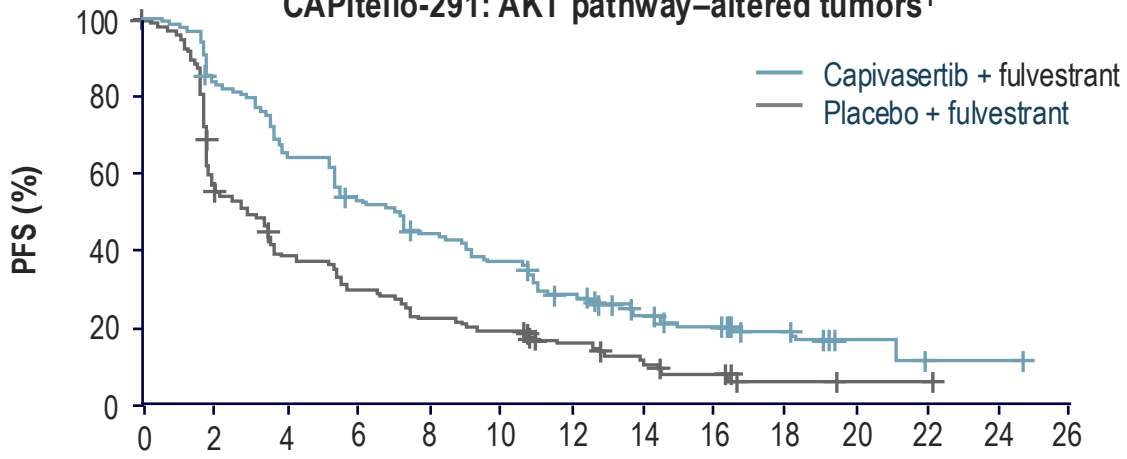
	Total[2] (n=119)	*ESR1*-mut[3] (n=27)	*ESR1*-wt[3] (n=75)
mPFS, mo [95% CI]	**8.0** [5.6–8.6]	**5.6** [3.8–12.0]	**8.3** [5.5–10.1]

[a]5.9% of patients had received prior CDK4/6i therapy for mBC.
ALPE, alpelisib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ER, estrogen receptor; ESR1, estrogen receptor 1 gene; FUL, fulvestrant; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; mut, mutation; PBO, placebo; (m)PFS, (median) progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; wt, wild type.
1. André F, et al. *N Engl J Med*. 2019;380(20):1929–1940; 2. Chia S, et al. ASCO 2023. Abstract P1078; 3. Turner S, et al. SABCS 2021. PD15-01.

CAPItello-291: Reduced mPFS benefit for capivasertib + fulvestrant in AKT-altered tumors with prior CDK4/6i as well as with prior chemotherapy

ESR1-mut data is not available

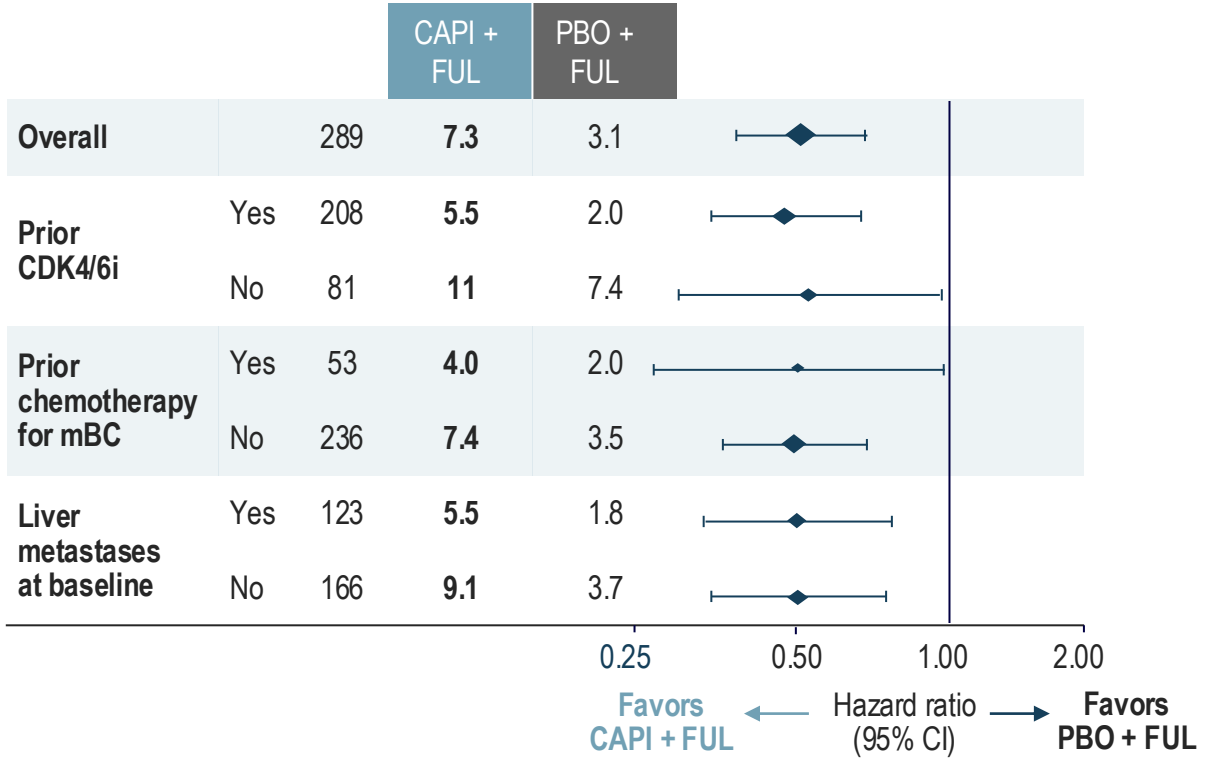
CAPItello-291: AKT pathway–altered tumors[1]



No. of patients														
CAPI + FUL	155	127	99	80	65	54	38	26	21	12	3	2	1	0
PBO + FUL	134	77	48	37	28	24	17	11	6	2	1	1	0	0

	CAPI + FUL (n=155)	PBO + FUL (n=134)
mPFS, mo[1] [95% CI]	**7.3** [5.5–9.0]	**3.1** [2.0–3.7]
Adjusted HR [95% CI]	**0.50** [0.38–0.65]	
Log-rank p-value	<0.001	

CAPItello-291: Impact of prior CDK4/6i therapy[2]



AKT, protein kinase B; CAPI, capivasertib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; chemo, chemotherapy; CI, confidence interval; ESR1, estrogen receptor 1 gene; FUL, fulvestrant; HR, hazard ratio; mBC, metastatic breast cancer; PBO, placebo; (m)PFS, (median) progression free survival.

1. Turner NC, et al. *N Engl J Med*. 2023;388(22):2058–2070; 2. Oliveira M, et al. *Ann Oncol*. 2023;8(1 suppl 4):101376 Poster 187O.

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Safety of ET combination regimens for second-line+, ER+/HER2− mBC

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

	mTOR inhibitors + ET		*PIK3CA* inhibitors + ET		AKT-pathway[a] inhibitors + ET	
	Everolimus[1]		Alpelisib[2]		Capivasertib[3]	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Adverse event incidence for combinations, %						
Neutropenia	–	–	–	–	–	–
Leukopenia	–	–	–	–	–	–
Anemia	16	6	–	–	10	2
Stomatitis	56	8	25	3	15	2
Rash	36	1	36	10	38	12
Diarrhea	30	2	58	7	72	9
Hyperglycemia	13	4	64	33	16	2
Fatigue	33	4	24	4	21	1
Nausea	29	0	45	3	35	1
Discontinuation rate, %	19		25		13	

PI3K/AKT/mTOR pathway inhibitors are associated with Grade 3/4 diarrhea, rash, hyperglycemia and stomatitis

[a]*PIK3CA/AKT1/PTEN*.

AKT, protein kinase B; ET, endocrine therapy; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; ; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog.

1. Baselga J, et al.*N Engl J Med*. 2012;366:520-529; 2. Andre F, et al. *N Engl J Med*. 2019;380:1929–1940; 3. Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070.

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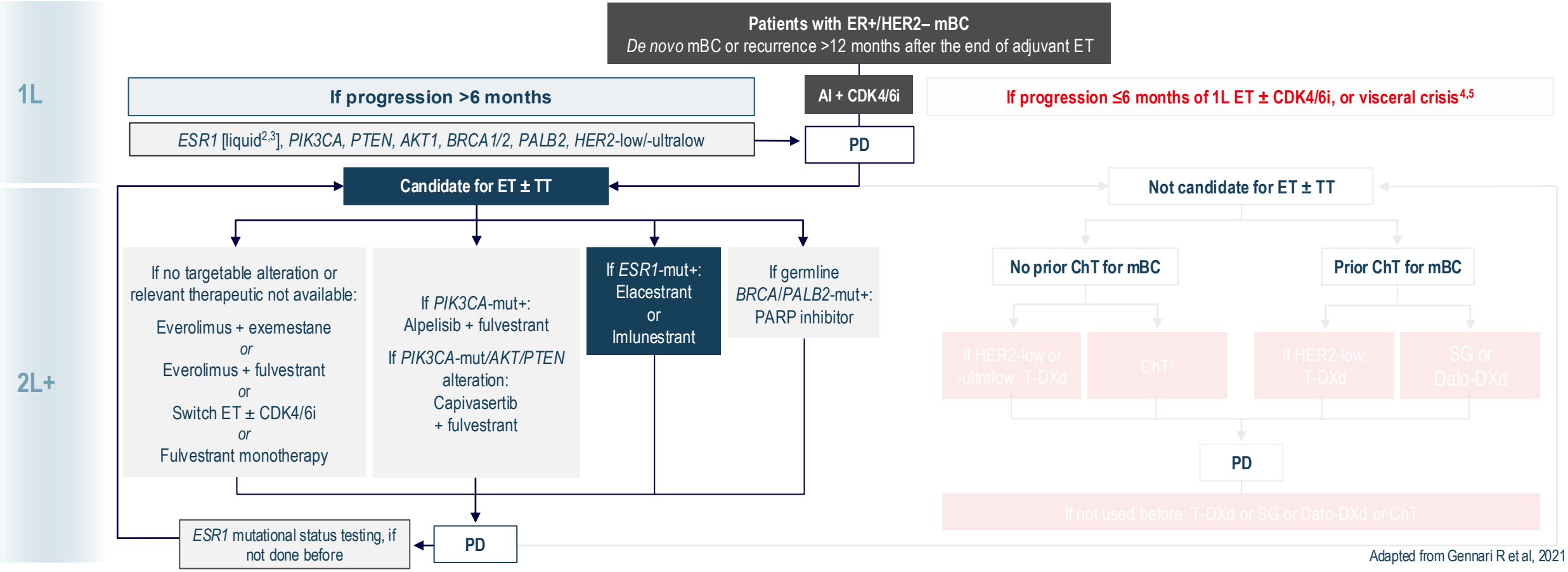
Second-line treatment choice is defined by the eligibility to receive endocrine therapy and driven by biomarker status



Adapted from Gennari R et al, 2021

[a]Taxane–bevacizumab or capecitabine–bevacizumab. 1L, first line; 2L+, second line and beyond; AI, aromatase inhibitor; AKT1, protein kinase B alpha; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ChT, chemotherapy; Dato-DXd, datopotamab deruxtecan; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mut+, mutation positive; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and TENsin homolog; SG, sacituzumab govitecan; SOC, standard of care; T-DXd, trastuzumab deruxtecan; TT, targeted therapy.

1. Adapted from: Gennari A, et al. *Ann Oncol*. 2021;32(12):1475–1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.2 April 2025 (Accessed July 2025); 2. Burstein HJ, et al. *J Clin Oncol*. 2023;41(18):3423–3425;
3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.4.2025. © *National Comprehensive Cancer Network*, Inc. 2025. All rights reserved. Accessed October 6, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org; 4. Bardia A, et al. *N Engl J Med*. 2024;391(22):2110–2122; 5. Cardoso F, et al. *Breast*. 2024;76:103756.

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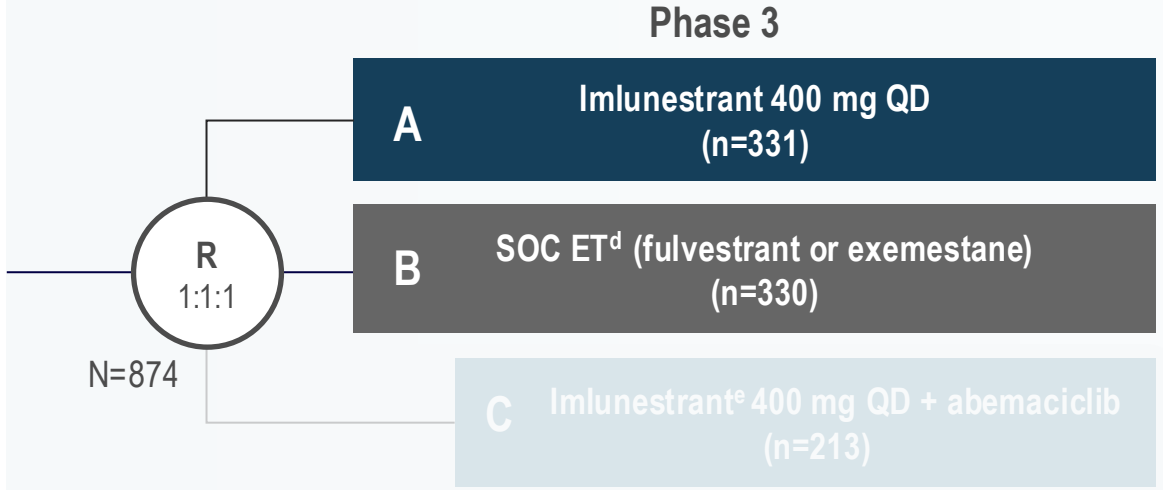
EMBER-3: Phase 3 trial of imlunestrant vs SOC or imlunestrant + abemaciclib[1]

Patient population

- Age ≥18 years old
- ER+/HER2- a/mBC
- Prior therapy:
  – Prior treatment with an AI, alone or in combination with a CDK4/6 inhibitor
  – No prior fulvestrant
  – No prior chemotherapy



Primary objectives:
Investigator-assessed PFS in *ESR1*-mut[a] patients (A vs B) and all patients (A vs B; C vs A)

Secondary objectives:
OS, PFS by BICR, ORR, safety

Stratification factors

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[f]

[a]*ESR1*-mut status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China, "Analysis conducted in all concurrently randomized patients; [b]Females must be postmenopausal (naturally, surgically, or ovarian function suppression); [c]Participants were expected to have prior treatment with a CDK4/6i if approved and could be reimbursed.[d]Investigator's choice, labeled dose; [e]Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B). [f]East Asia vs United States/European Union vs others. AKT, protein kinase B; BICR, blinded independent central review; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor, *ESR1*, estrogen receptor 1 gene; ET endocrine therapy; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; m, mutation; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PR, progesterone receptor; QD, once daily; R, randomization; SERD, selective estrogen receptor degrader; SOC ET, standard of care endocrine therapy.

1. Jhaveri KL, et al. *N Engl J Med.* 2025;392(12):1189-1202.

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EMBER-3: Baseline demographics in *ESR1*-mut patient population[1]

65% prior CDK4/6 inhibitors, 21% treatment in 1L

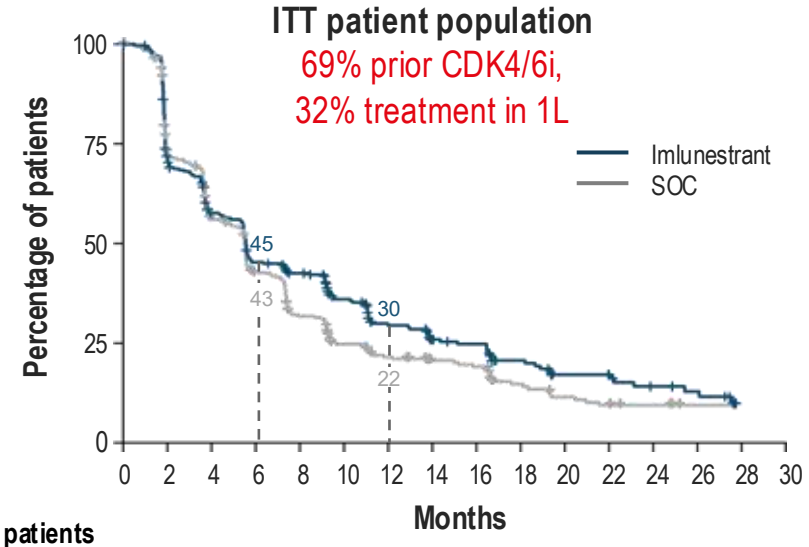
Characteristic		Imlunestrant n=138	SOC ET n=118
Median age, years (range)		61 (28-85)	60 (33-85)
Post-menopausal, %		89	89
Region, %	East Asia North America/Western Europe Other	22 46 33	22 46 32
Visceral metastases, %		61	57
ESR1-mut, %[a]		100	100
PI3K pathway mutations, %		52	48
Prior chemotherapy, %		**NO**	**NO**
Prior fulvestrant, %		**NO**	**NO**
Primary endocrine resistance, %		**NO**	**NO**
Most recent ET, %	As (neo) adjuvant therapy For aBC	21 73	20 77
Prior CDK4/6i, %	Overall As adjuvant therapy For aBC	67 2 65	72 3 70

[a]ESR1-mut status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China, "Analysis conducted in all concurrently randomized patients."
1L, first line; aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA; ESR1, estrogen receptor 1 gene; ET endocrine therapy; mut, mutation; PI3K, phosphoinositide 3-kinase; PR, progesterone receptor; SOC, standard of care.

1. Jhaveri KL, et al. *N Engl J Med.* 2025;392(12):1189–1202.

Table adapted from Jhaveri KL et al, 2025

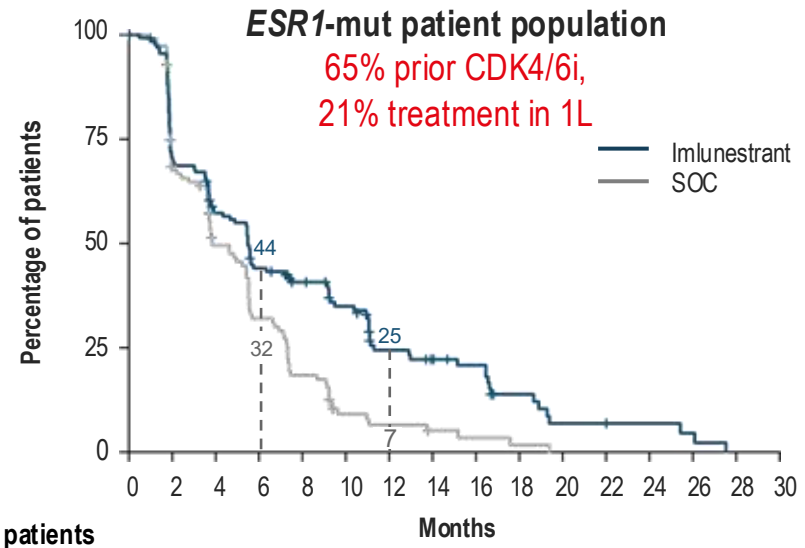
EMBER-3: Imlunestrant monotherapy has no mPFS benefit in ITT patient population; mPFS benefit is shown in patients with *ESR1*-mut[1,2]



No. of patients

IMLU	331	225	173	135	118	89	62	47	43	30	20	19	13	10	0	0
SOC	330	221	165	122	89	63	51	41	38	23	17	14	10	2	0	0

	IMLU (n=331)	SOC (n=330)
mPFS, mo	5.6	5.5
Absolute difference	+0.1	
HR [95% CI]	**0.87** [0.72–1.04], P=0.12	
	NEGATIVE	



No. of patients

IMLU	138	95	74	56	45	35	22	18	15	8	4	4	3	2	0	0
SOC	118	74	51	33	19	7	5	3	2	1	0	0	0	0	0	0

	IMLU (n=138)	SOC (n=118)
mPFS, mo	5.5	3.8
Absolute difference	+1.7	
HR [95% CI]	**0.62** [0.46–0.82], P<0.001[2]	
	POSITIVE	

[a]Baseline characteristic for patients in the imlunestrant arm only; based on line of most recent endocrine therapy.
1/2L, first/second line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ESR1, estrogen receptor 1 gene; HR, hazard ratio; IMLU, imlunestrant; mPFS, median progression-free survival; OS, overall survival; SOC, standard of care.

1. Jhaveri KL, et al. *N Engl J Med.* 2025;392(12):1189–1202; 2. Jhaveri KL, et al. SABCS 2024. Abstract GS1-01.

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EMBER-3: The safety profiles of imlunestrant were consistent with previous findings[1]

	Imlunestrant (n=327)		SOC ET (n=324)	
Adverse events in ≥10% of patients, %	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Fatigue	23	<1	13	1
Diarrhea	21	<1	12	0
Nausea	17	<1	13	0
Arthralgia	14	1	14	<1
AST increased	13	1	13	1
Back pain	11	1	7	<1
ALT increased	10	<1	10	1
Anemia	10	2	13	3

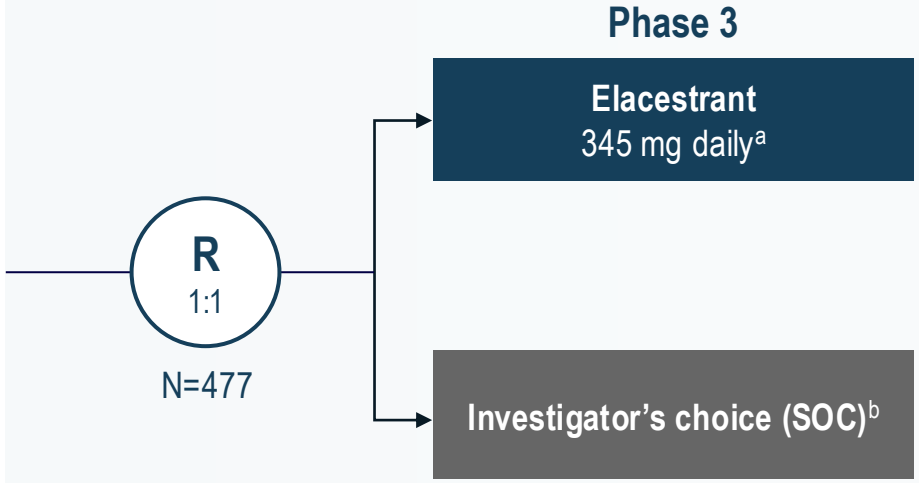
ALT, Alanine aminotransferase AST, aspartate aminotransferase; ET, endocrine therapy; SOC, standard of care.

1. Jhaveri KL, et al. *N Engl J Med.* 2025;392(12):1189–1202.

EMERALD: Phase 3 trial of elacestrant vs SOC endocrine therapy[1]

Patient population

- Age ≥18 years old
- ER+/HER2– a/mBC
- Prior therapy:
  - 1–2 lines of ET
  - CDK4/6i required
  - Primary resistance allowed
  - Prior fulvestrant allowed
  - Prior chemotherapy allowed



Primary objectives:
PFS in *ESR1*-mut;
PFS in all patients

Secondary objectives:
OS, PFS, ORR, DOR, CBR, SD, safety and tolerability

Stratification factors

- *ESR1*-mut status
- Presence of visceral metastases
- Prior treatment with fulvestrant

[a]345 mg of elacestrant is equivalent to 400 mg of elacestrant dihydrochloride. [b]Fulvestrant, anastrozole, letrozole, exemestane.
a/mBC, advanced/metastastic breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mut, mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; SD, stable disease; SOC, standard of care.

1. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246–3256.

EMERALD: Baseline characteristics[1]

ESR1-mut patient population included 100% prior CDK4/6i, 70% visceral disease, 37% treatment as 3rd line, 24% prior fulvestrant, 23% prior chemotherapy

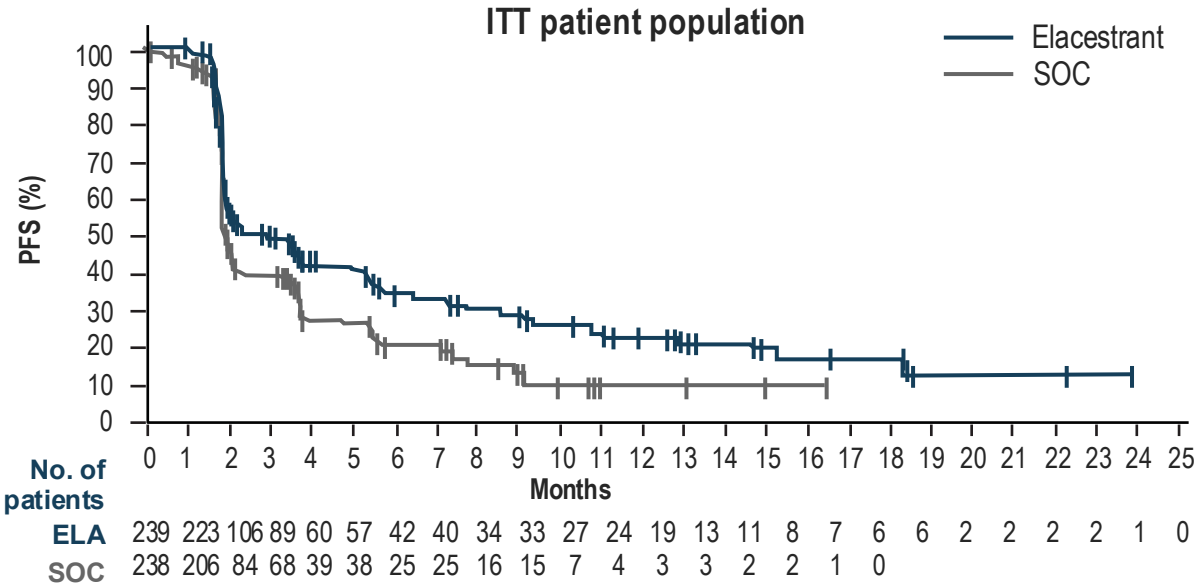
	Elacestrant		SOC	
	All (n=239)	*ESR1*-mut (n=115)	All (n=238)	*ESR1*-mut (n=113)
Median age, years (range)	63 (24-89)	64 (28-89)	64 (32-83)	63 (32-83)
Female, n (%)	233 (97.5)	115 (100)	237 (99.6)	113 (100)
ECOG PS, n (%)				
0	143 (59.8)	67 (58.3)	135 (56.7)	62 (54.9)
1	96 (40.2)	48 (41.7)	103 (43.3)	51 (45.1)
Visceral metastasis[a], n (%)	163 (68.2)	81 (70.4)	169 (71.1)	84 (74.3)
Prior CDK4/6i, n (%)	239 (100)	115 (100)	238 (100)	113 (100)
Line of therapy in mBC, n (%)				
2nd line	129 (54.0)	73 (63.5)	141 (59.2)	69 (61.1)
3rd line	110 (46.0)	42 (36.5)	97 (40.8)	44 (38.9)
Prior therapies for advanced or metastatic disease, n (%)				
Fulvestrant	70 (29.3)	27 (23.5)	75 (31.5)	28 (24.8)
Aromatase inhibitor	193 (80.8)	101 (87.8)	194 (81.1)	96 (85.0)
Tamoxifen	19 (7.9)	9 (7.8)	15 (6.3)	9 (8.0)
No. of prior lines of chemotherapy in a/mBC, n (%)	26 (20.1)	26 (22.6)	58 (24.4)	32 (28.3)

[a]Includes lung, liver, brain, pleural, and peritoneal involvement.

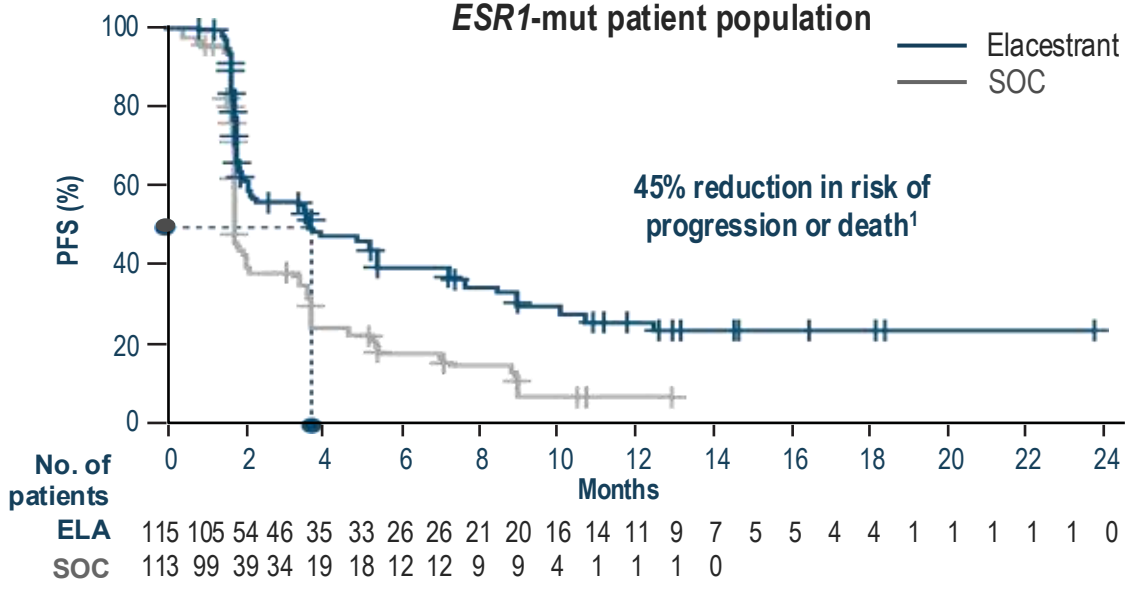
a/mBC, advanced/metastatic breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; mut, mutation; SOC, standard of care.

1. Adapted from Bidard FC, et al. *J Clin Oncol*. 2022;40(28):3246–3256.

EMERALD: Elacestrant shows statistically significant results for both ITT and *ESR1*-mut patient populations[1]



	Elacestrant (n=239)	SOC (n=238)
mPFS, mo	2.8	1.9
Absolute difference, mo	+0.9	
HR [95% CI]	0.70 [0.55–0.88], P=0.0018	
	POSITIVE	



	Elacestrant (n=115)	SOC (n=113)
mPFS, mo	3.8	1.9
Absolute difference, mo	+1.9	
HR [95% CI]	0.55 [0.39–0.77], P=0.005	
	POSITIVE	

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; Ela, elacestrant; ESR1, estrogen receptor 1 gene; ET, endocrine therapy; HR, hazard ratio; ITT, intent to treat; (m)PFS, (median) progression-free survival; SOC, standard of care.

1. Bidard FC, et al. *J Clin Oncol*. 2022;40(28):3246–3256.

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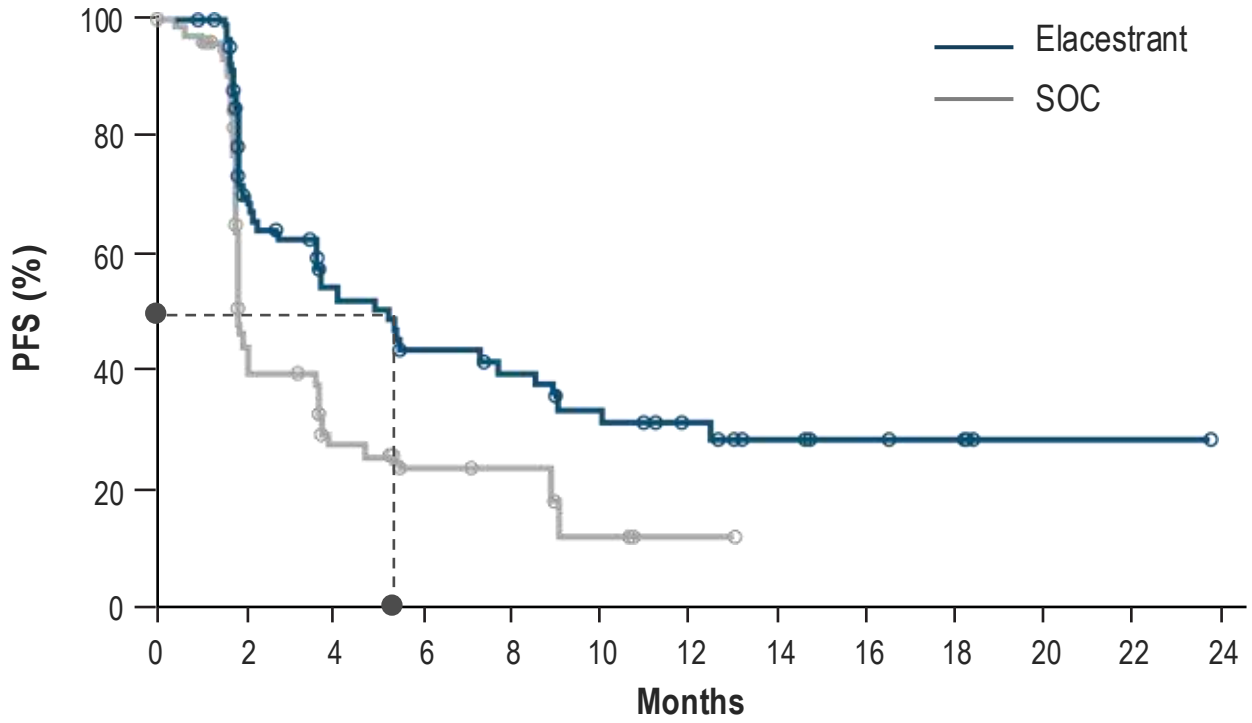
EMERALD: Elacestrant shows improved mPFS in *ESR1*-mut population with no prior chemotherapy[1]

Post-hoc analysis



	Elacestrant (n=89)	SOC (n=81)
mPFS, mo	**5.3**	**1.9**
Absolute difference, mo	**+3.4**	
HR [95% CI][a]	**0.54** [0.36–0.80], P=0.00235	

[a]Calculated with covariates.

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; Ela, elacestrant; ESR1, estrogen receptor 1 gene; ET, endocrine therapy; HR, hazard ratio; (m)PFS, (median) progression-free survival; SOC, standard of care.

1. Kaklamani V, et al. *J Clin Oncol*. 2022;40(16 suppl): Abstract 1100.

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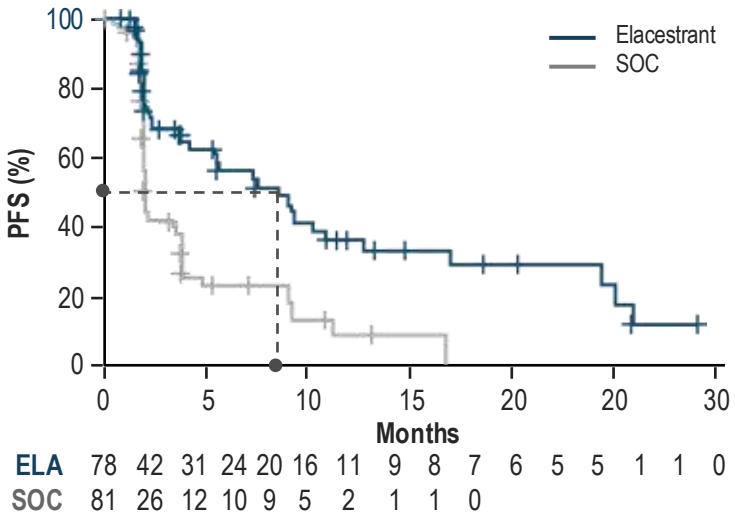
EMERALD: Elacestrant shows an 8.6 mPFS in *ESR1*-mut patient population whose tumors retained endocrine sensitivity[1–3]

mPFS was 7.3 mo in patients with liver and/or lung mets, and 5.5 mo in those with *ESR1* and *PIK3CAmut* tumors[1,2]

Post-hoc analysis ≥12 months duration of prior ET + CDK4/6i[1,2]



	Elacestrant (n=78)	SOC (n=81)
mPFS, mo	8.6	1.9
Absolute difference, mo	+6.7	
HR [95% CI]	0.41 [0.26–0.63]	

Patients with ≥12 months of prior ET + CDK4/6i	% (n)	Elacestrant mPFS, months	SOC mPFS, months	HR [95% CI]
All *ESR1*-mut patients	**100** (159)	**8.6**	**1.9**	**0.41** [0.26–0.63]
PIK3CA-mut[a]	**39** (62)	**5.5**	**1.9**	**0.42** [0.18–0.94]
Bone metastases[b]	**86** (136)	**9.1**	**1.9**	**0.38** [0.23–0.62]
Liver and/or lung metastases[c]	**71** (113)	**7.3**	**1.9**	**0.35** [0.21–0.59]
≥3 metastatic sites[d]	**33** (53)	**10.8**	**1.8**	**0.31** [0.12–0.79]
TP53-mut	**38** (61)	**8.6**	**1.9**	**0.30** [0.13–0.64]
HER2−low expression[e]	**48** (77)	**9.0**	**1.9**	**0.30** [0.14–0.60]

Calculated with covariates. This was an exploratory analysis. Post-hoc analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.
[a]Includes 545K, H1047R, E542K, and others. [b]85% of patients had bone and other sites of metastases (30% of these patients had no liver or lung involvement). [c]55% of patients had liver and other sites of metastases (10% of these patients had no lung or bone involvement); 25% of patients had lung and other sites of metastases (2% of these patients had no liver or bone involvement). [d]The number of metastatic sites was available for 135 of 159 patients with ESR1-mutated tumors and prior ET + CDK4/6i ≥12 months. [e]Locally assessed HER2 immunohistochemistry score of 1+ and 2+ with no in situ hybridization amplification. Data not available for all patients.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ESR1, estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mPFS, median progression-free survival; mut, mutation; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SOC, standard of care; TP53, tumor protein 53.

1. Bardia A, et al. *Clin Cancer Res*. 2024;30(19):4299–4309; 2. Bardia A, et al. SABCS 2022. Abstract GS3–01; 3. Bardia A, et al. SABCS 2024. P1-01-25.

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Elacestrant real-world data

- Elacestrant is the first oral SERD approved in patients with *ESR1*-mut ER+/ HER2– mBC, based on results from the EMERALD clinical study, showing improved PFS HR 0.55 (95% CI 0.39–0.77)[1]
- Real-world insights are valuable for affirming the efficacy benefit of elacestrant in current clinical practice.

Two different RWE studies were performed:

1. *Clinical and genomic factors associated with elacestrant outcomes in ESR1-mut mBC*[1]

   Guardant Health (*Maxwell R. Lloyd, Azka Ali, Caroline M. Weipert, Sheila R. Solomon, Jayati Saha, Marla Lipsyc-Sharf, Erika P. Hamilton, Kevin Kalinsky, Adam Brufsky, Aditya Bardia, Nicole Zhang, Seth A. Wander*)

2. *Real-world outcomes of elacestrant in ER+/HER2−, ESR1-mut mBC*[2]

   Komodo/Foundation Medicine* *(Hope S. Rugo, Virginia Kaklamani, Heather McArthur, Seth A. Wander, William Gradishar, Reshma Mahtani, Mark Pegram, Maryam Lustberg, Elyse Swallow, Jessica Maitland, Sebastian Kloss, Tomer Wasserman, and Sara M. Tolaney)*

*Komodo Research Dataset linked with Foundation Medicine Inc. clinical genomic data.

CI, confidence interval; ER, estrogen receptor; *ESR1,* estrogen receptor 1 gene; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; mBC, metastatic breast cancer; PFS, progression-free survival; RWE, real-world evidence; rwPFS, real world progression-free survival; SERD, selective estrogen receptor degrader.

1. Lloyd M, et al. *Clin Cancer Res.* 2026; https://doi.org/10.1158/1078-0432.CCR-25-3033; 2. Rugo HS, et al. *Clin Cancer Res.* 2026; https://doi.org/10.1158/1078-0432.CCR-25-3040.

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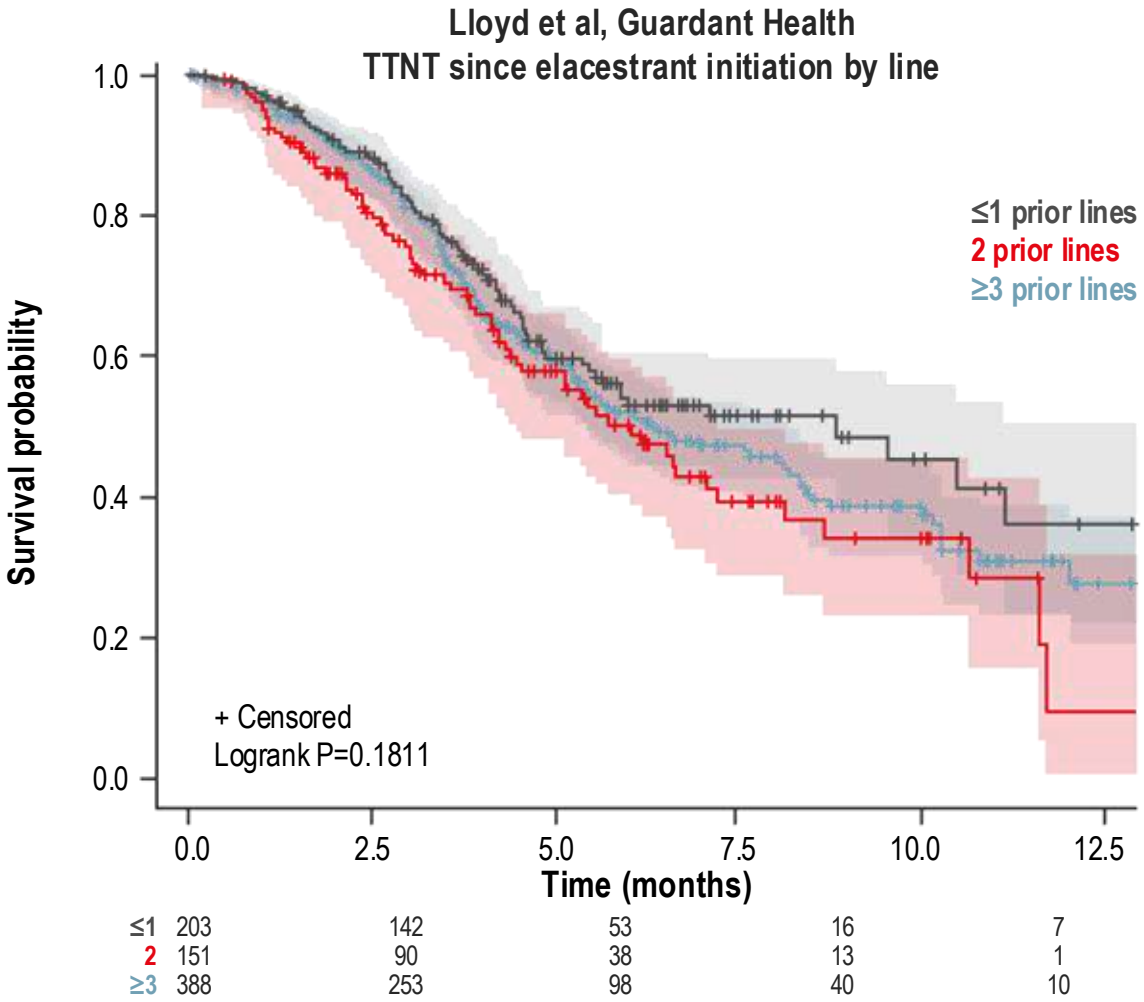
Clinical and genomic factors associated with elacestrant outcomes in *ESR1-mut* mBC[1]



Adjusted HR, ≤1 prior *lines as reference*, (95% CI):

- 2 prior lines: 1.34 (0.96–1.87)
- ≥3 prior lines: 1.12 (0.85–1.48)

Prior lines	≤1	2	≥3
Subjects	203	151	388
Event	77	70	165
Censored	126	81	233
Median TTNT	**8.833**	**6.033**	**6.333**
95% CL	5.467–	4.467–7.200	5.433–8.200

Patients treated in earlier lines (i.e., ≤1 prior line of therapy) had a longer TTNT

Observational retrospective analyses are not intended for direct comparisons with clinical trials.

2L, second line; CI, confidence interval; CL, confidence limits; HR, hazard ratio; TTNT, time-to-next-treatment.

1. Lloyd M, et al. *Clin Cancer Res.* 2026; https://doi.org/10.1158/1078-0432.CCR-25-3033

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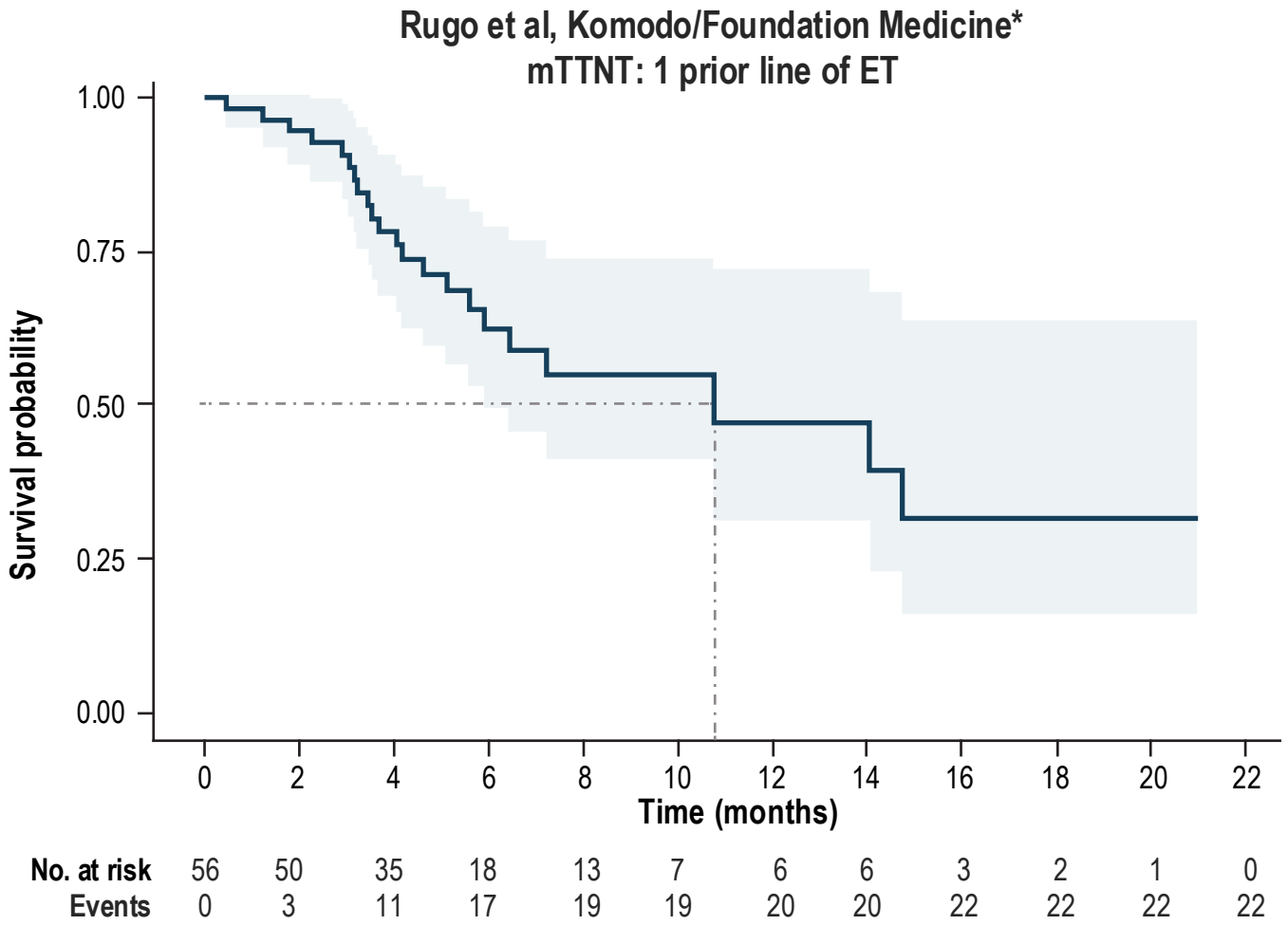
Real-world outcomes of elacestrant in ER+/HER2−, *ESR1*-mut mBC[1]



	2L (n=56)
Events, n (%)	22 (39.3)
Median TTNT, mo [95% CI]	**10.8** [5.9–NR]

This was an exploratory analysis. RWE analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.
*Komodo Research Dataset linked with Foundation Medicine Inc. clinical genomic data
CI, confidence interval; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; NR, not reached; RWE, real-world evidence; rwPFS, real-world progression-free survival.
1. Rugo HS, et al. *Clin Cancer Res.* 2026; https://doi.org/10.1158/1078-0432.CCR-25-3040.

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Similar real-world outcomes were observed with elacestrant in patients with ER+/HER2-, *ESR1*-mut mBC in clinically relevant subgroups

Including 1-2 prior lines of ET, visceral metastasis (including liver) and patients harboring coexisting *ESR1* and PI3K-pathway mutations

	Real-World Data Rugo et al. Komodo/Foundation Medicine[1,c]		Real-World Data Lloyd et al. Guardant Health[2]		Phase 3 EMERALD Bardia et al. Subgroup Analysis[3]	
Median efficacy outcomes across patient subgroups	**N**	**mTTNT**	**N**	**mTTNT**	**N**	**mPFS**
1-2 prior lines of ET ± CDK4/6i	128	**8.2**	–	–	–	–
1-2 prior lines of ET ± CDK4/6i ≥12 months	116	**8.4**	–	–	78	**8.6**
1 prior line of ET ± CDK4/6i	56	**10.8**	104	**8.8**	–	–
2 prior lines of ET ± CDK4/6i	72	**7.7**	144	**5.9**	–	–
≥3 prior lines of ET ± CDK4/6i	172	**7.5**	492	**6.4**	–	–
Visceral metastasis	266	**7.9**	–	–	–	–
Liver metastases	138	**7.2**	–	–	–	–
Liver and/or lung metastases	–	**–**	–	–	56	**7.3**
Coexisting *ESR1* and PI3K pathway mutations[a,b]	130	**6.3**	234	**5.2**	27	**5.5**
All patients with no prior chemotherapy	153	**8.4**	–	–	–	–
All patients with no prior fulvestrant	85	**12.9**	347	**7.7**	–	–

Observational retrospective analysis are not intended for direct comparisons with clinical trials

[a] Includes patients with *ESR1* mutation variants (Y537C and/or Y537N and/or Y537S and/or D538G and/or E380Q) and PIK3CA mutation variants (H1047 and/or E545 and/or E542), AKT alteration, or PTEN loss of function.
[b] EMERALD subgroup analysis includes patients with *ESR1*- and *PIK3CA*-mutated tumours; [c] Komodo Research Dataset linked with Foundation Medicine Inc. clinical genomic data. CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; *ESR1*, estrogen receptor 1; mBC, metastatic breast cancer; mPFS, median progression-free survival; mTTNT, median time to next treatment; Ph, phase; PI3K, phosphoinositide 3-kinase

1. Rugo HS, et al. *Clin Cancer Res.* 2026; https://doi.org/10.1158/1078-0432.CCR-25-3040; 2.Lloyd M, et al. *Clin Cancer Res.* 2026; https://doi.org/10.1158/1078-0432.CCR-25-3033; 3. Bardia A, et al. Clin Cancer Res. 2024;30(19):4299–430

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After CDK4/6i, elacestrant single agent in patients with *ESR1* and *PIK3CA* co-mutations delivers similar benefit to combination therapies with PI3K/AKTi

	Bardia et al, EMERALD CCR (n=27)[1] *mPFS (months)*	Lloyd et al, Guardant Health (n=234)[2] *mTTNT (months)*	Rugo et al, Komodo/Foundation Medicine[a] (n=130)[3] *mTTNT (months)*	Rugo et al, BYLieve (n=27)[4] *mPFS (months)*	Turner et al, CAPItello-291 (n=113)[5] *mPFS (months)*
	Elacestrant	Elacestrant	Elacestrant	Alpelisib + fulvestrant	Capivasertib + fulvestrant
Prior CDK4/6i Only *AKT/PIK3CA*-mut	N/A	N/A	N/A	**8.1**	**5.5**
Prior CDK4/6i *AKT/PIK3CA*-mut *AND* *ESR1*-mut	**5.5**	**5.2[b]**	**6.3[c]**	**5.6**	N/A

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies.

This was an exploratory analysis. RWE analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.

[a] Komodo Research Dataset linked with Foundation Medicine Inc. clinical genomic data; [b]76% of all patients (n=573) received prior CDK4/6i therapy; [c] 89.9% of all patients (n=275) received prior CDK4/6i therapy.

AKT, protein kinase B; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ESR1, estrogen receptor 1; mPFS, median progression-free survival; mTTNT, median real-world time to next treatment; mut, mutation; N/A, not applicable; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RWE, real-world evidence.

1. Bardia A, et al. *Clin Cancer Res*. 2024;30:4299-4309; 2. Lloyd M, et al. *Clin Cancer Res* 2026; https://doi.org/10.1158/1078-0432.CCR-25-3033; 3. Rugo HS, et al. *Clin Cancer Res* 2026; https://doi.org/10.1158/1078-0432.CCR-25-3040.; 4. Rugo HS, et al. *Lancet Oncol*. 2021;22(4):489–498; 5. Oliveira M, et al. *Ann Oncol*. 2023;8(1 suppl 4):10 1376 Poster 187O.

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EMERALD: Safety[1]

Most common adverse events ≥10% in either arm in the overall population[1]

Adverse events[1,a]	Elacestrant (n=237)		SOC (n=230)	
	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)
Nausea	35	2.5	19	0.9
Vomiting[b]	19	0.8	9	0
Diarrhea	13	0	10	1
Constipation	12	0	6	0
Abdominal pain[b]	11	1	10	0.9
Dyspepsia	10	0	2.6	0
Fatigue[b]	26	2	27	1
Decreased appetite	15	0.8	10	0.4
Headache	12	2	12	0
Hot flush	11	0	8	0

Nausea summary[1]	Elacestrant (n=237)	SOC (n=230)
Grade 3 nausea, %	2.5	0.9
Dose-reduction rate due to nausea, %	1.3	NA
Discontinuation rate due to nausea, %	1.3	0
Antiemetic use, %*	8.0	10.3 (AI) 3.7 (fulvestrant)

Nausea was generally reported early, with a median time to first onset of 14 days.[2]
*Patients who received fulvestrant may have been on antiemetics prior to enrollment.[1]

- No patient experienced Grade 4 nausea or vomiting with elacestrant[1]
- Treatment-related AEs leading to discontinuation were 3.4% and 0.9% in the elacestrant and SOC arms, respectively[1]
- **No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia[1]**

[a]Adverse events were graded using NCI CTCAE version 5.0. [b]Includes other related terms.
AE, adverse events; AI, aromatase inhibitor; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SOC, standard of care (fulvestrant or AI).
1. Bardia A, et al. *Clin Cancer Res*. 2024;30(19):4299–4309; 2. Stemline. ORSERDU (elacestrant) SmPC. 2024.

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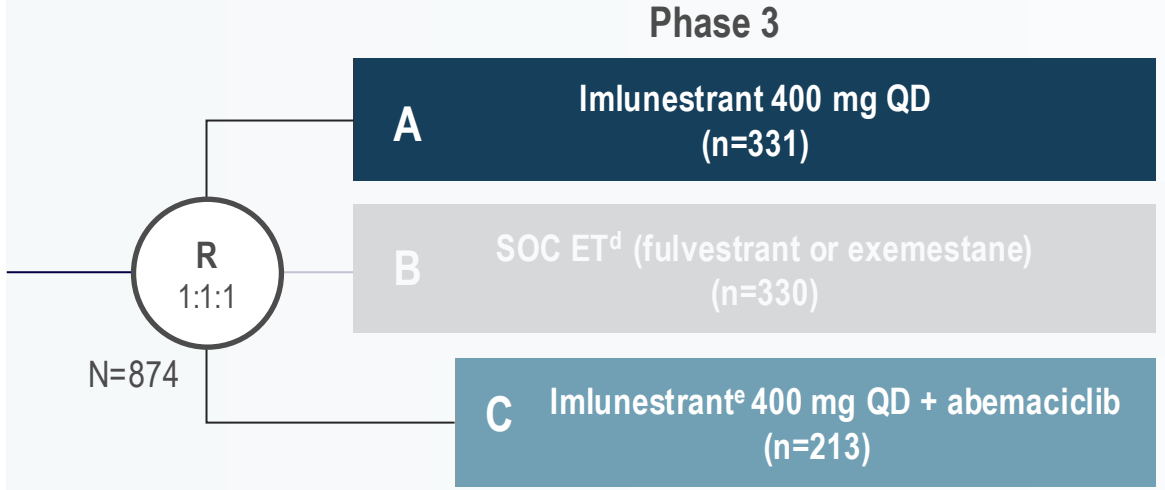
Oral SERD combination studies
EMBER-3: Phase 3 trial of imlunestrant vs imlunestrant + abemaciclib[1]

Patient population

- Age ≥18 years old
- ER+/HER2- a/mBC
- Prior therapy:
  – Prior treatment with an AI, alone or in combination with a CDK4/6 inhibitor
  – No prior fulvestrant
  – No prior chemotherapy



Primary objectives:
Investigator-assessed PFS in *ESR1*-mut[a] patients (A vs B) and all patients (A vs B; C vs A)

Secondary objectives:
OS, PFS by BICR, ORR, safety

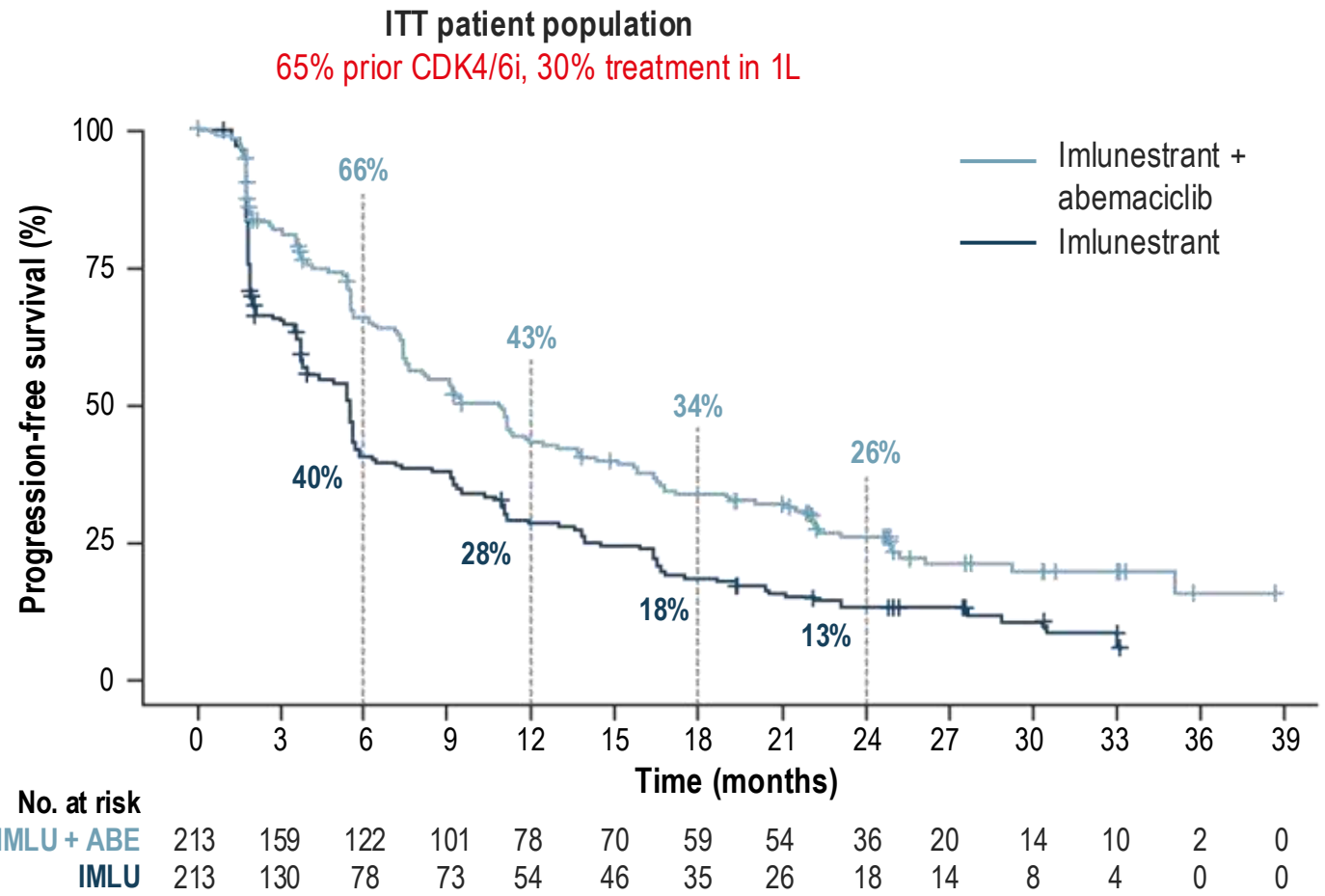
Stratification factors

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[f]

[a]*ESR1*-mut status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China, "Analysis conducted in all concurrently randomized patients; [b]Females must be postmenopausal (naturally, surgically, or ovarian function suppression); [c]Participants were expected to have prior treatment with a CDK4/6i if approved and could be reimbursed.[d]Investigator's choice, labeled dose; [e]Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B). [f]East Asia vs United States/European Union vs others. AKT, protein kinase B; BICR, blinded independent central review; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor, *ESR1*, estrogen receptor 1 gene; ET endocrine therapy; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; m, mutation; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PR, progesterone receptor; QD, once daily; R, randomization; SERD, selective estrogen receptor degrader; SOC ET, standard of care endocrine therapy.

1. Jhaveri KL, et al. *N Engl J Med.* 2025;392(12):1189-1202.

EMBER-3: Imlunestrant plus abemaciclib[1,2]



Combination not yet approved by the FDA/EMA

	IMLU + ABE (n=213)	IMLU (n=213)
mPFS, mo	**10.9**	**5.5**
Absolute difference, mo	**+4.4**	
HR [95% CI]	**0.59** [0.47–0.74], P<0.0001	

ABE, abemaciclib; CI, confidence interval; HR, hazard ratio; IMLU, imlunestrant; mPFS, median progression-free survival; OS, overall survival.

1. Jhaveri KL, et al. *N Engl J Med.* 2025;392(12):1189–1202; 2. Jhaveri KL et al. SABCS 2025.Abstrac GS3-08.

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EMBER-3: The safety profiles of imlunestrant + abemaciclib were consistent with previous findings[1]

	Imlunestrant + abemaciclib (n=208)		SOC ET (n=324)	
Adverse events in ≥20% of patients, %	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Diarrhea	86	8	12	0
Nausea	49	2	13	0
Neutropenia	48	20	5	2
Anemia	44	8	13	3
Fatigue	39	5	13	1
Vomiting	31	1	5	<1
Leukopenia	26	4	5	0
Hypercreatinemia	22	1	2	0
Abdominal pain	20	2	6	<1
Decreased appetite	20	1	4	<1

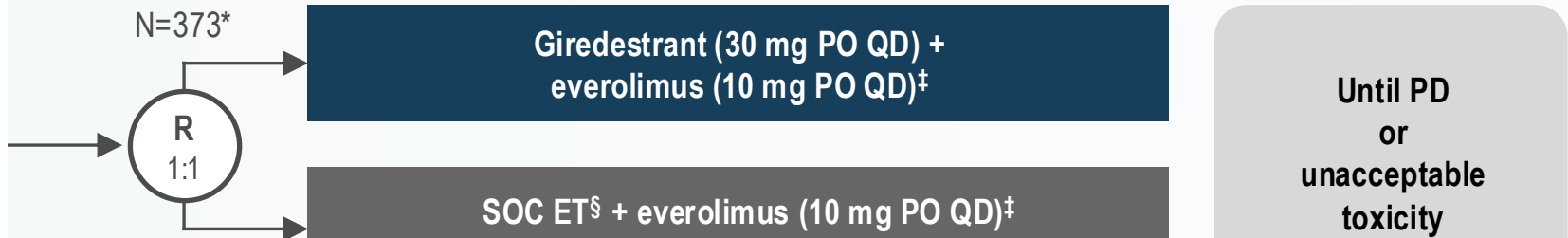
ALT, Alanine aminotransferase AST, aspartate aminotransferase; ET, endocrine therapy; SOC, standard of care.

1. Jhaveri KL, et al. *N Engl J Med.* 2025;392(12):1189–1202.

Oral SERD combination studies
evERA: Phase 3 trial of giredestrant + everolimus vs SOC ET + everolimus[1]

Key eligibility criteria*

- ER+, HER2– aBC (1–3L of therapy)
- ≤2 prior lines of ET in the aBC setting
- PD or relapse during/post-CDK4/6i + ET†
- No prior chemotherapy in the aBC setting
- Measurable disease per RECIST v1.1 or evaluable bone metastases



‡ Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol[1]

* Trial was enriched to 55% of patients with *ESR1*m at baseline (centrally tested via circulating tumour DNA)
† Patients had to receive ≥6 months of CDK4/6i + ET in the aBC setting to be eligible for enrolment; prior fulvestrant was allowed

Stratification factors

- ≤2 Prior treatment with fulvestrant (yes vs no)
- *ESR1*m (yes vs no/indeterminate)
- Site of disease (visceral [lung and/or liver involvement] vs non-visceral)

Co-primary endpoints (RECIST v1.1):

- INV-PFS in patients whose tumors had *ESR1*m
- INV-PFS in the ITT population

Key secondary endpoints:

- OS
- INV-ORR, DoR

Exploratory endpoints:

- Clinical and biomarker subgroup analyses

1–3L, first- to third-line; ABC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER+, estrogen receptor–positive; ESR1m, ESR1 mutation; ET, endocrine therapy; HER2−, HER2-negative; INV, investigator-assessed; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, orally; QD, once daily; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumours; SOC ET, standard of care endocrine therapy.

1. Rugo HS, et al. SABCS 2025. Abstract GS3-09; 2. Rugo HS, et al. *Lancet Oncol.* 2017;18:654–662.

evERA: Phase 3 trial baseline characteristics[1]

	Giredestrant + everolimus n=183	SOC ET + everolimus n=190
Median age, years (range)	62.0 (27–83)	60.0 (28–84)
Female sex, n (%)	182 (99.5)	187 (98.4)
Race, n (%)		
White	103 (56.3)	119 (62.6)
Asian	66 (36.1)	57 (30.0)
Black	9 (4.9)	9 (4.7)
Other	5 (2.7)	5 (2.6)
Region, n (%)		
North America	69 (37.7)	75 (39.5)
Asia–Pacific	58 (31.7)	49 (25.8)
Western Europe	36 (19.7)	43 (22.6)
Other	20 (10.9)	23 (12.1)
Visceral disease, n (%)*	126 (68.9)	131 (68.9)
Disease involvement in liver	89 (48.6)	100 (52.9)
Post-menopausal at screening, n (%)	156 (85.2)	159 (83.7)

	Giredestrant + everolimus n=183	SOC ET + everolimus n=190
***ESR1*m, n (%)†**	102 (55.7)	105 (55.3)
***PIK3CA/AKT1/PTEN* alteration, n (%)†,‡**	82 (44.8)	80 (42.1)
*PIK3CA*m	64 (35.0)	51 (26.8)
AKT1 E17K alteration	14 (7.7)	12 (6.3)
PTEN alteration	13 (7.1)	28 (14.7)
Duration of prior CDK6/6i§		
<12 mo	44 (24.0)	50 (26.3)
≥12 mo	136 (74.3)	135 (71.0)
12 to <24 mo	61 (33.3)	60 (31.6)
≥24 mo	75 (41.0)	75 (39.5)
Prior CDK4/6i, n (%)	183 (100)	190 (100)
Palbociclib	104 (56.8)	119 (62.6)
Ribociclib	52 (28.4)	54 (28.4)
Abemaciclib	53 (29.0)	49 (25.8)
Prior fulvestrant, n (%)	86 (47.0)	89 (46.8)
First line with CDK4/6i	53 (29.0)	42 (22.1)

* Visceral disease is defined as any lung and/or liver involvement. Detected at baseline by central assessment; † Not mutually exclusive; PIK3CAm included activating mutations; PTEN alterations included pathogenic short variants and copy number loss; § Most recent line of CDK4/6i for mBC. Patients had to receive ≥6 months of CDK4/6i + ET in the ABC setting to be eligible for enrollment.

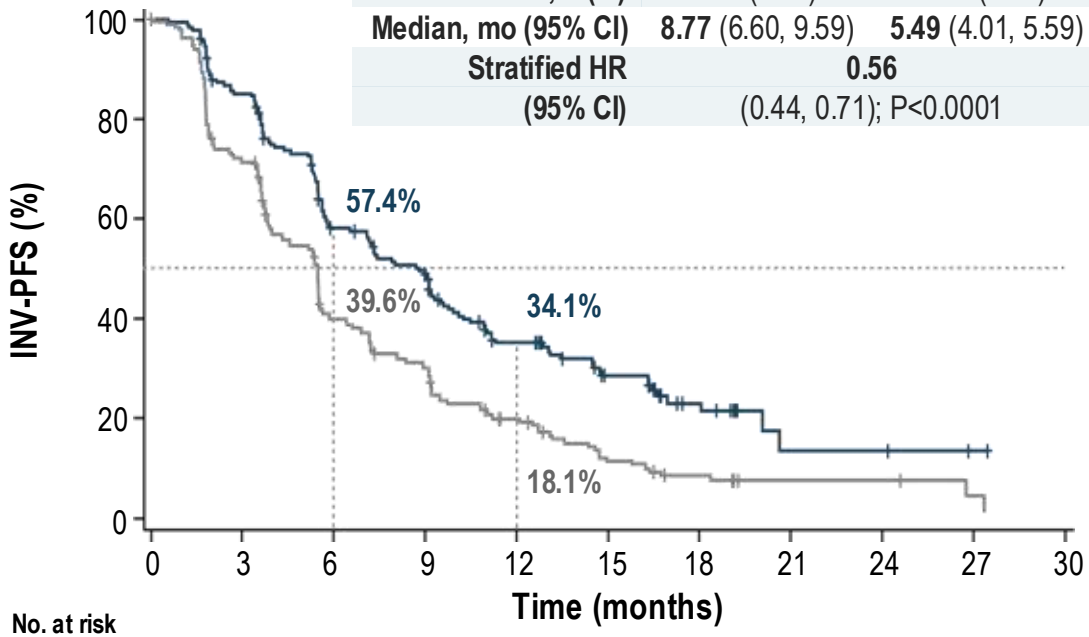
ABC, advanced breast cancer; AKT1, AKT serine/threonine kinase 1; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*m, ESR1 mutation; ET, endocrine therapy; ITT, intention to treat; mBC, metastatic breast cancer; mo, months; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PIK3CAm, PIK3CA mutation; PTEN, phosphatase and tensin homolog; SOC ET, standard-of-care endocrine therapy.

1. Rugo HS, et al. SABCS 2025. Abstract GS3-09.

evERA: Phase 3 trial co-primary endpoints, INV-PFS in the ITT and *ESR1*-mut populations[1]

ITT patient population

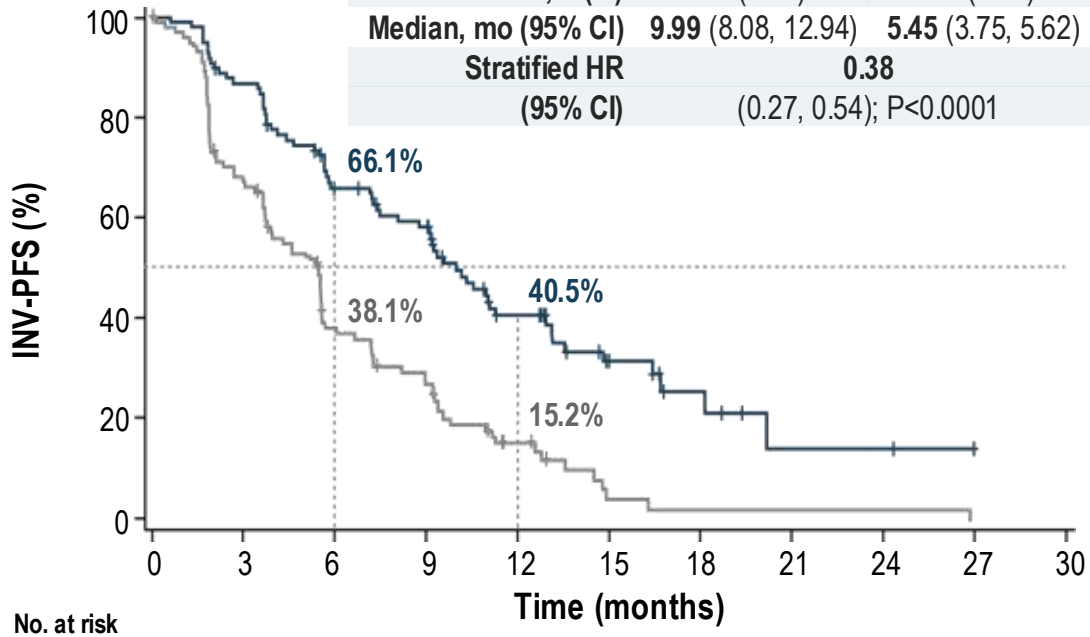
	Giredestrant + everolimus (n=183)	SOC ET + everolimus (n=190)
Events, n (%)	126 (68.9)	163 (85.8)
Median, mo (95% CI)	**8.77** (6.60, 9.59)	**5.49** (4.01, 5.59)
Stratified HR	**0.56**	
(95% CI)	(0.44, 0.71); P<0.0001	



No. at risk										
Giredestrant + everolimus	183	149	95	70	47	29	14	3	3	1
SOC ET + everolimus	190	131	68	50	27	14	7	3	3	1

ESR1-mut patient population

	Giredestrant + everolimus (n=102)	SOC ET + everolimus (n=105)
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	**5.45** (3.75, 5.62)
Stratified HR	**0.38**	
(95% CI)	(0.27, 0.54); P<0.0001	



No. at risk										
Giredestrant + everolimus	102	85	61	52	28	13	6	2	2	
SOC ET + everolimus	105	67	35	25	10	2	1	1	1	

Combination not yet approved by the FDA/EMA

Data cutoff: July 16, 2025. Median follow-up in the ITT population was 18.4 mo in the giredestrant + everolimus arm and 18.7 mo in the SOC ET + everolimus arm.
CI, confidence interval; ESR1m, ESR1 mutation; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; ITT, intention to treat; mo, months; SOC ET, standard-of-care endocrine therapy.

1. Rugo HS, et al. SABCS 2025. Abstract GS3-09.

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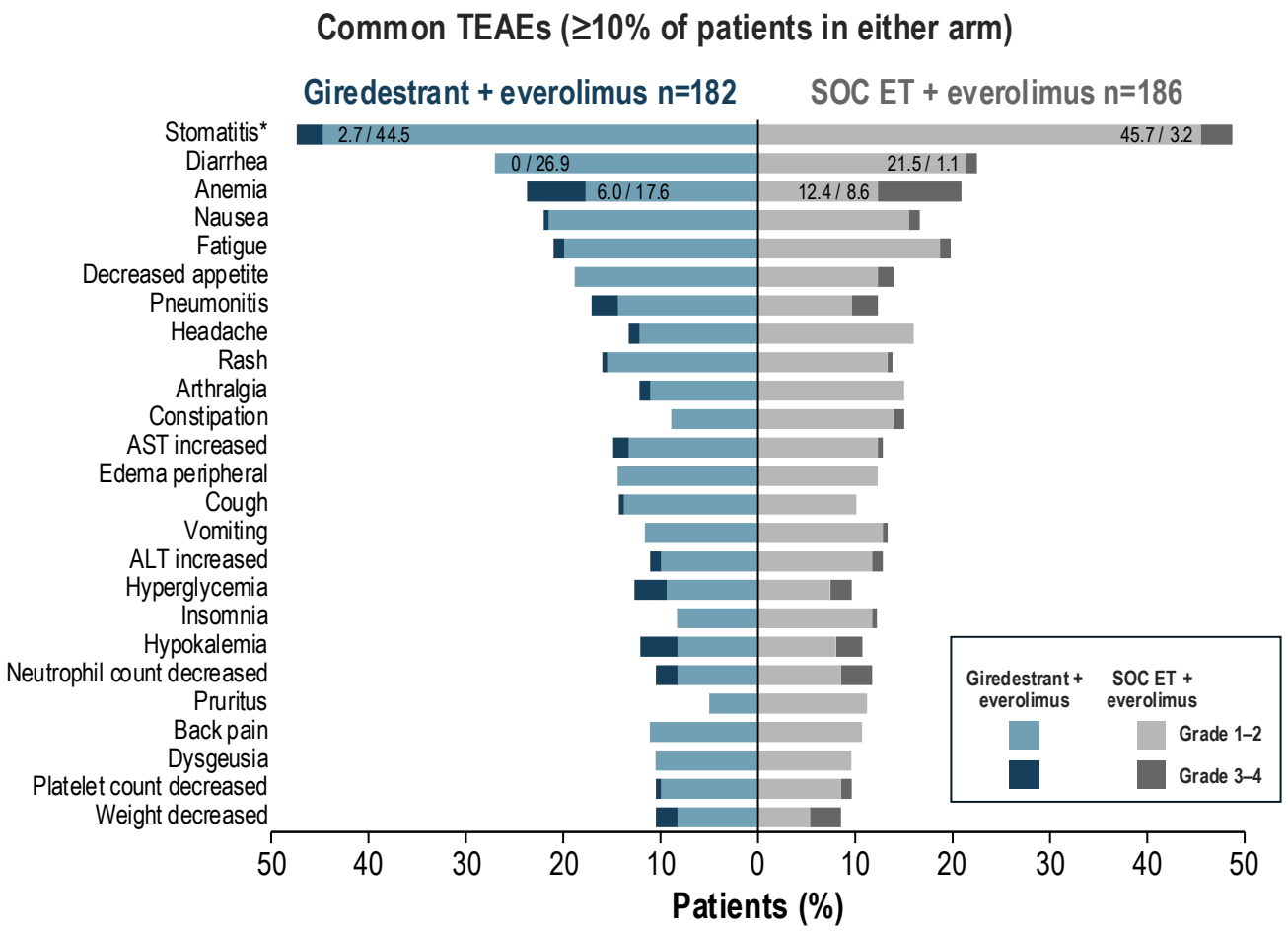
evERA: Phase 3 trial adverse event overview[1]



Safety overview

Patients with AE, n (%)	Giredestrant + everolimus (n=182)	SOC ET + everolimus (n=186)
AEs with fatal outcome†	5 (2.7)	5 (2.7)
AEs leading to everolimus dose reduction	56 (30.8)	49 (26.3)
AEs leading to discontinuation of treatment§		
Giredestrant or SOC	15 (8.2)	12 (6.5)
Everolimus	31 (17.0)	22 (11.8)
Any	31 (17.0)	22 (11.8)

Selected AEs

Patients with AE, n (%)	Giredestrant + everolimus (n=182)		SOC ET + everolimus (n=186)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Bradycardia¶	7 (3.8)	0	1 (0.5)	0
Photopsia	0	0	0	0

Data cutoff: 16 July 2025.

* Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol (Rugo HS, et al. Lancet Oncol. 2017;18:654–662); † Fatal AEs (bold = related) were pneumonia (n=3; 1 related), intestinal perforation (n=1), and death (n=1) in the giredestrant + everolimus arm, and pneumonia, cholecystitis infective, erysipelas, sepsis, and hypoxic–ischaemic encephalopathy (n=1 each) in the SOC ET + everolimus arm;
‡ Dose reduction of giredestrant was not permitted; no dose reductions of SOC ET were reported; § Comparable across both arms when adjusted per 100 patient-years to account for differences in treatment exposure;
¶ Assessed as a medical concept using grouped terms; all events were Grade 1, non-serious, and no treatment interruptions/interventions were needed. All events had resolved by data cutoff.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOC ET, standard-of-care endocrine therapy; TEAE, treatment-emergent adverse event.

1. Rugo HS, et al. SABCS 2025. Abstract GS3-09.

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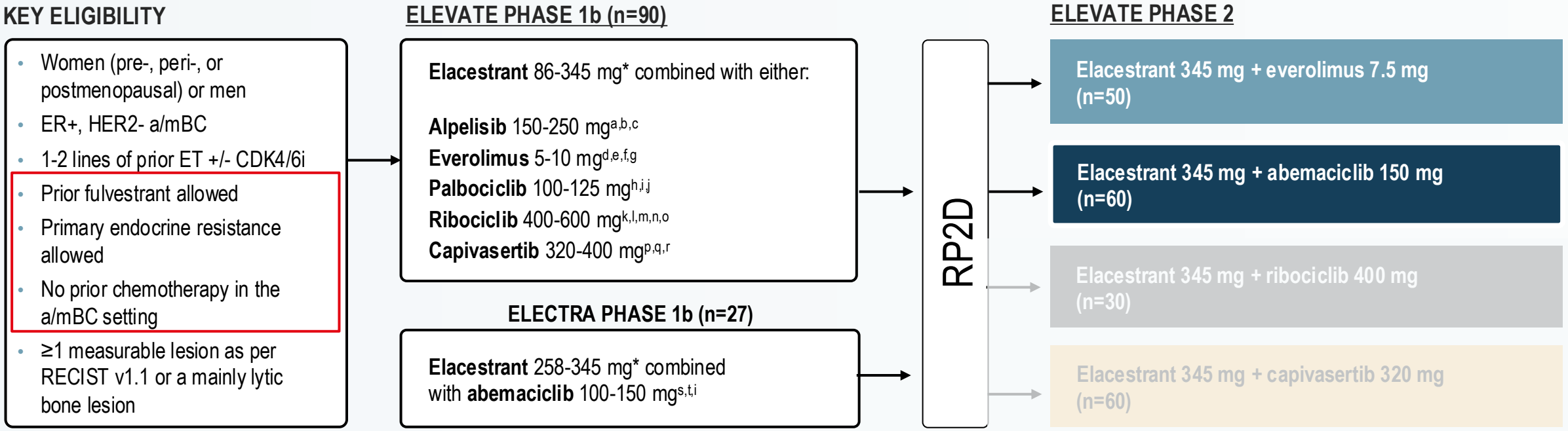
Ongoing oral SERD combination studies
ELEVATE: Phase 2 trial of elacestrant combination regimens[1,2]



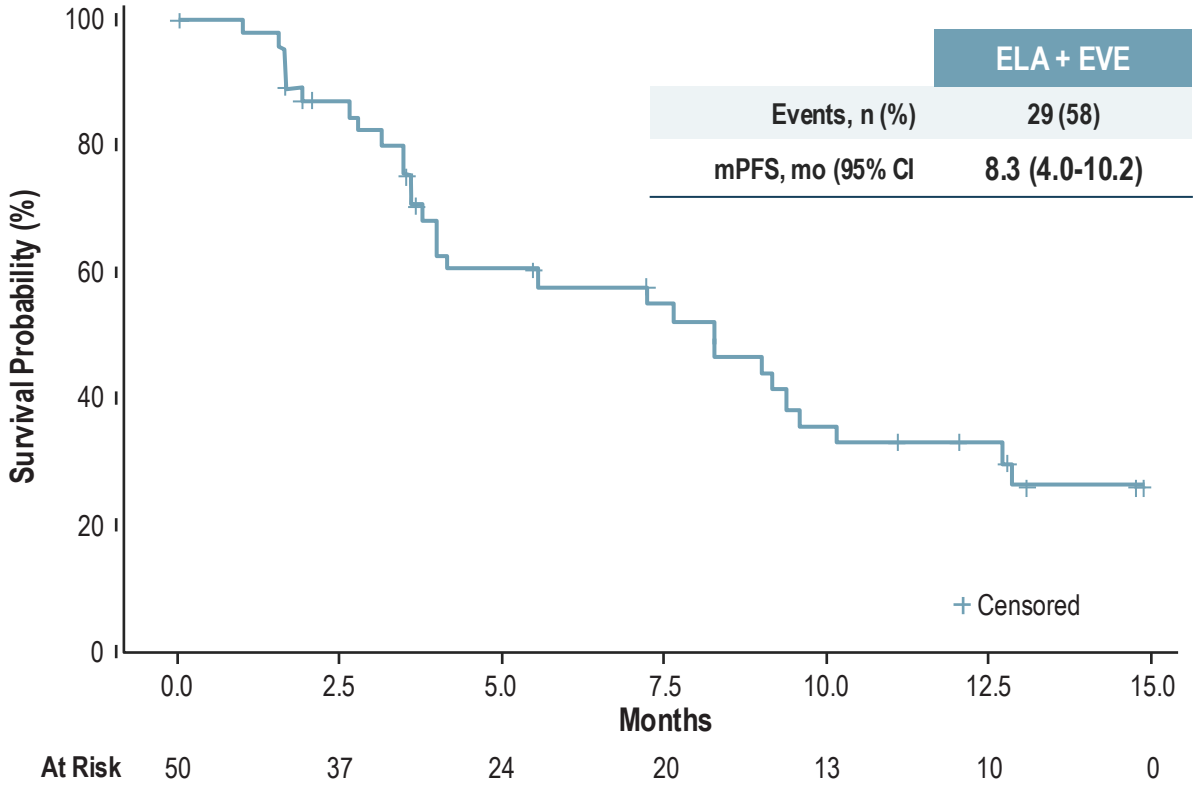
Phase 2 Objectives

Primary: PFS (RECIST v1.1)
Secondary: ORR, DoR, CBR, PFS, OS, and safety

Elacestrant 86 mg is equivalent to 100 mg elacestrant hydrochloride; elacestrant 172 mg is equivalent to 200 mg elacestrant hydrochloride; elacestrant 258 mg is equivalent to 300 mg elacestrant hydrochloride; elacestrant 345 mg is equivalent to 400 mg elacestrant hydrochloride. [a]Elacestrant 258 mg + alpelisib 250 mg (cohort 1); [b]Elacestrant 258 mg* + alpelisib 200 mg (cohort -1); [c]Elacestrant 258 mg* + alpelisib 150 mg (cohort -2); [d]Elacestrant 258 mg* + everolimus 5 mg (cohort 1); [e]Elacestrant 345 mg* + everolimus 5 mg (cohort 2); [f]Elacestrant 345 mg* + everolimus 10 mg (cohort 3); [g]Elacestrant 345 mg* + everolimus 7.5 mg (cohort 4); [h]Elacestrant 258 mg* + palbociclib 100 mg (cohort 1); [i]Elacestrant 345 mg* + palbociclib 100 mg (cohort 2); [j]Elacestrant 345 mg* + palbociclib 125 mg (cohort 3); [k]Elacestrant 86 mg* + ribociclib 400 mg (cohort 1); [l]Elacestrant 172 mg* + ribociclib 400 mg (cohort 2); [m]Elacestrant 258 mg* + ribociclib 400 mg (cohort 3); [n]Elacestrant 172 mg* + ribociclib 600 mg (cohort 4); [o]Elacestrant 345 mg* + ribociclib 400 mg (cohort 5); [p]Elacestrant 258 mg* + capivasertib 320 mg (cohort 1); [q]Elacestrant 345 mg* + capivasertib 320 mg (cohort 2); [r]Elacestrant 345 mg* + capivasertib 400 mg (cohort 3); [s]Elacestrant 258 mg* + abemaciclib 100 mg (cohort 1); [t]Elacestrant 345 mg* + abemaciclib 100 mg (cohort 2); [i]Elacestrant 345 mg* + abemaciclib 150 mg (cohort 3); a/mBC, advanced or metastatic breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; n, number; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; v, version.

1. Open-Label Umbrella Trial to Evaluate Safety and Efficacy of Elacestrant in Various Combination in Patients With Metastatic Breast Cancer (ELEVATE). ClinicalTrials.gov. May 20, 2024. Accessed August 26, 2024. https://clinicaltrials.gov/trial/NCT05563220; 2. A Phase 1b/2, Open-Label Umbrella Trial to Evaluate Safety and Efficacy of Elacestrant in Various Combinations in Patients with Metastatic Breast Cancer (ELEVATE). STML-ELA-0222. Updated December 22, 2023.

ELEVATE: Phase 2 trial of elacestrant + everolimus mPFS results in all patients and key subgroups[1]



	ELA + EVE
Events, n (%)	29 (58)
mPFS, mo (95% CI	8.3 (4.0-10.2)

	Elacestrant + everolimus	
Subgroup	**n**	**mPFS, months (95% CI)**
All patients	50	**8.3** [4.0–10.2]
Visceral disease	36	**7.7** [3.7–9.4]
No prior fulvestrant	25	**8.3** [4.2–12.9]
No primary endocrine resistance	40	**8.3** [4.0–12.9]
ESR1-mut	21	**8.3** [3.5–12.9]
ESR1-wt	27	**9.0** [4.2–12.7]
PIK3CA-mut	25	**8.3** [3.6–10.2]
PIK3CA-wt	23	**9.4** [4.0–NR]

Follow Up Time, median (95% CI), months: 4.1 (3.6–8.3)

Elacestrant + everolimus showed a consistent PFS benefit across all subgroups

Key clinical characteristics: Prior CDK4/6i 100%, Visceral metastases 72%, Primary ET resistance 20%, *ESR1m* 42%, *PIK3CAm* 50%, Prior fulvestrant 50%

Data cut-off: Sept 15, 2025. CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; Ela, elacestrant; ESR1m, estrogen receptor 1 mutation; ET, endocrine therapy; Eve, everolimus; mo, months; mPFS, median progression-free survival; n, number; NR, not reached; PIK3CAm, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutation; PFS, progression-free survival; wt, wild-type.

1. Open-Label Umbrella Trial to Evaluate Safety and Efficacy of Elacestrant in Various Combination in Patients With Metastatic Breast Cancer (ELEVATE). ClinicalTrials.gov. May 20, 2024. Accessed August 26, 2024. https://clinicaltrials.gov/trial/NCT05563220.

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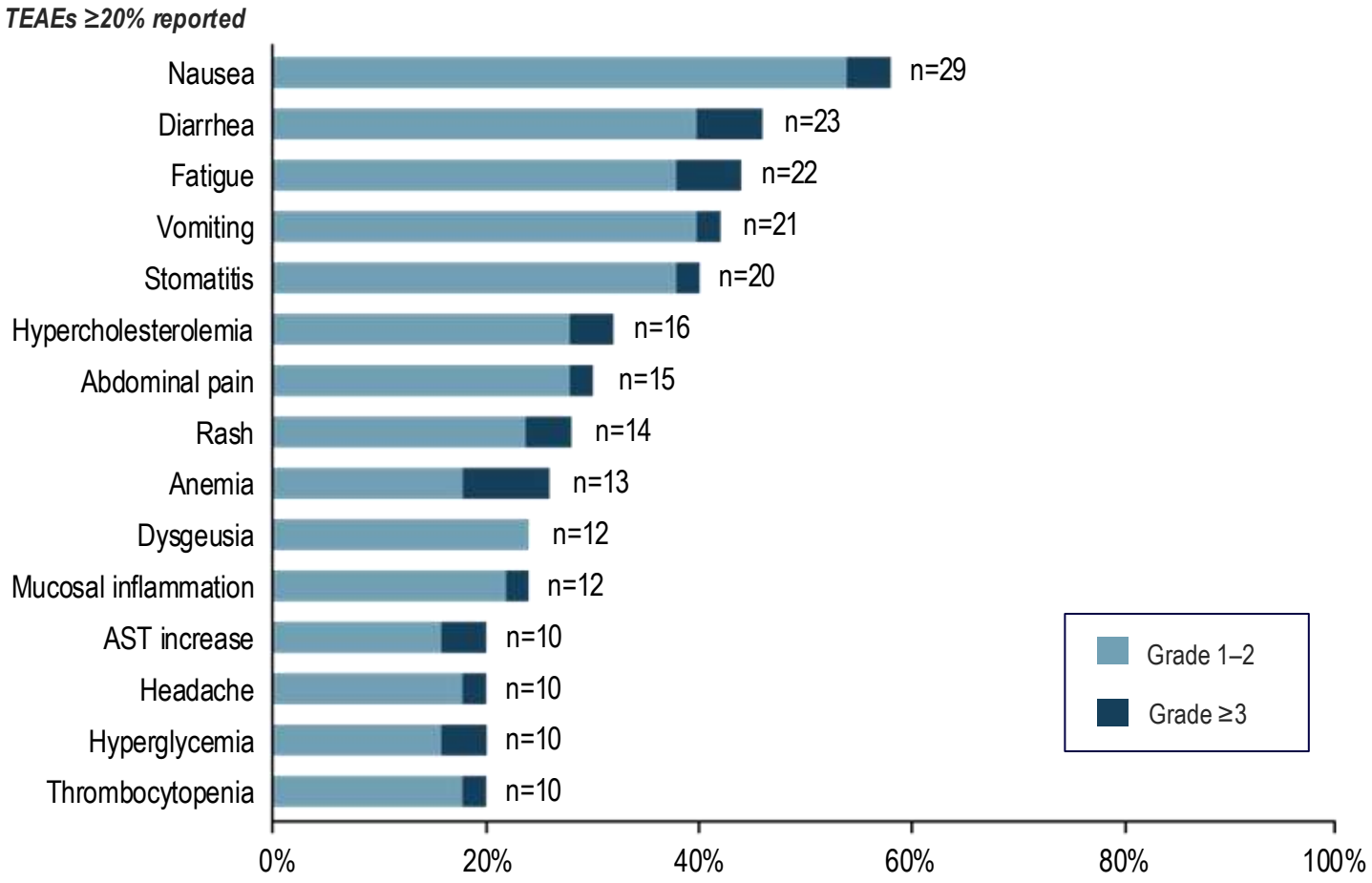
ELEVATE: Phase 2 trial of elacestrant + everolimus adverse events[1]



- The safety profile is consistent with either everolimus plus standard ET or elacestrant
- No bradycardia or photopsia were reported, and no new safety signals were observed
- Any TEAE leading to elacestrant + everolimus drug withdrawal 6%
- Any TEAE leading to elacestrant + everolimus drug dose reduction 2%

Data cut-off: Sept 15, 2025. TEAEs, Treatment-emergent adverse events; AST, aspartate aminotransferase.

1. Open-Label Umbrella Trial to Evaluate Safety and Efficacy of Elacestrant in Various Combination in Patients With Metastatic Breast Cancer (ELEVATE). ClinicalTrials.gov. May 20, 2024. Accessed August 26, 2024. https://clinicaltrials.gov/trial/NCT05563220.

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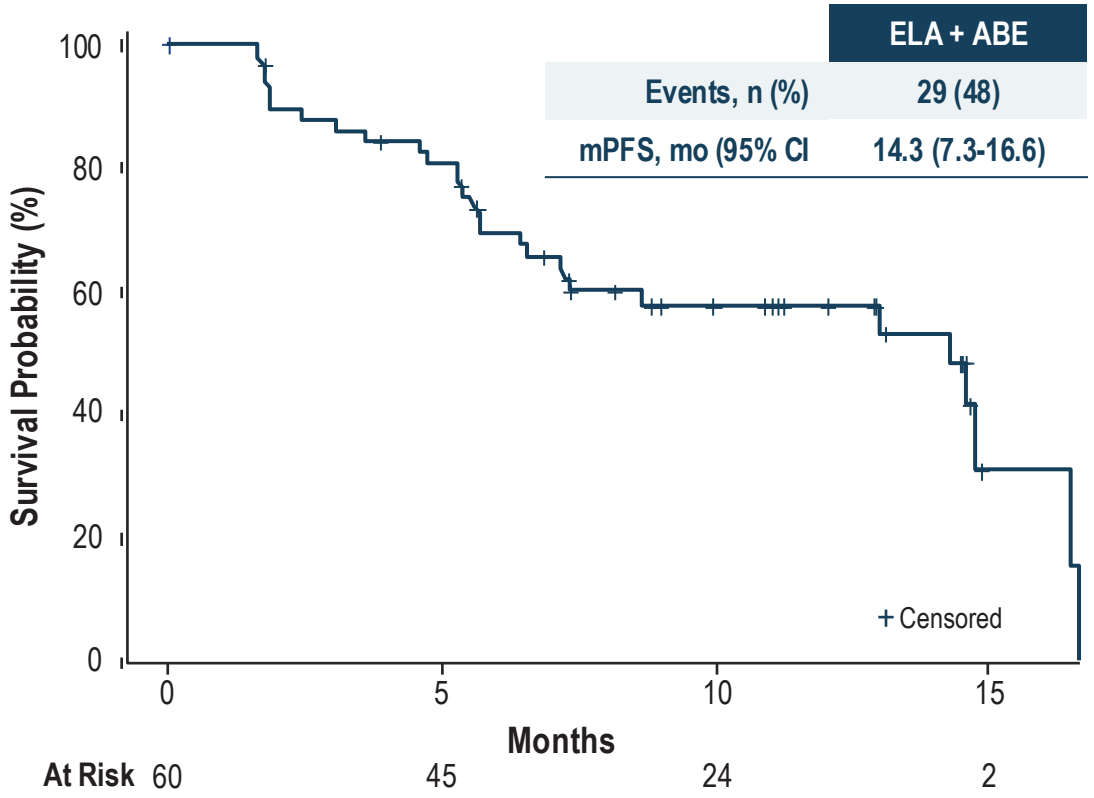
ELEVATE: Phase 2 trial of elacestrant + abemaciclib mPFS results in all patients and key subgroups[1]



	Elacestrant + abemaciclib	
Subgroup	N	mPFS, months (95% CI)
All patients	60	**14.3** [7.3–16.6]
Visceral disease	55	**14.3** [7.4–16.6]
No prior fulvestrant	42	**14.8** [8.7–NR]
No primary endocrine resistance	51	**14.3** [7.3–16.6]

Follow Up Time, median (95% CI), months: Overall: 8.6 (6.5–12.6) – Arm C: 5.7 (4.6–8.7) – Arm D: 11.6 (8.5–13.4)

Maturity not reached for PFS (95% CI) for genomic subgroups (*ESR1* / *PIK3CA*) or by prior CDK4/6i exposure

Elacestrant + abemaciclib showed a consistent PFS benefit across all subgroups

Key clinical characteristics: Visceral metastases 92%, primary ET resistance 15%, *ESR1m* 33% (10/23), *PIK3CA*m 27%, Prior CDK4/6i 50%, Prior fulvestrant 30%

Data cut-off: Sept 15, 2025. Abema, abemaciclib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; Ela, elacestrant; ESR1m, estrogen receptor 1 mutation; ET, endocrine therapy; mo, months; mPFS, median progression-free survival; n, number; NR, not reached; PFS, progression-free survival; PIK3CAmut, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutation.

1. Open-Label Umbrella Trial to Evaluate Safety and Efficacy of Elacestrant in Various Combination in Patients With Metastatic Breast Cancer (ELEVATE). ClinicalTrials.gov. May 20, 2024. Accessed August 26, 2024. https://clinicaltrials.gov/trial/NCT05563220.

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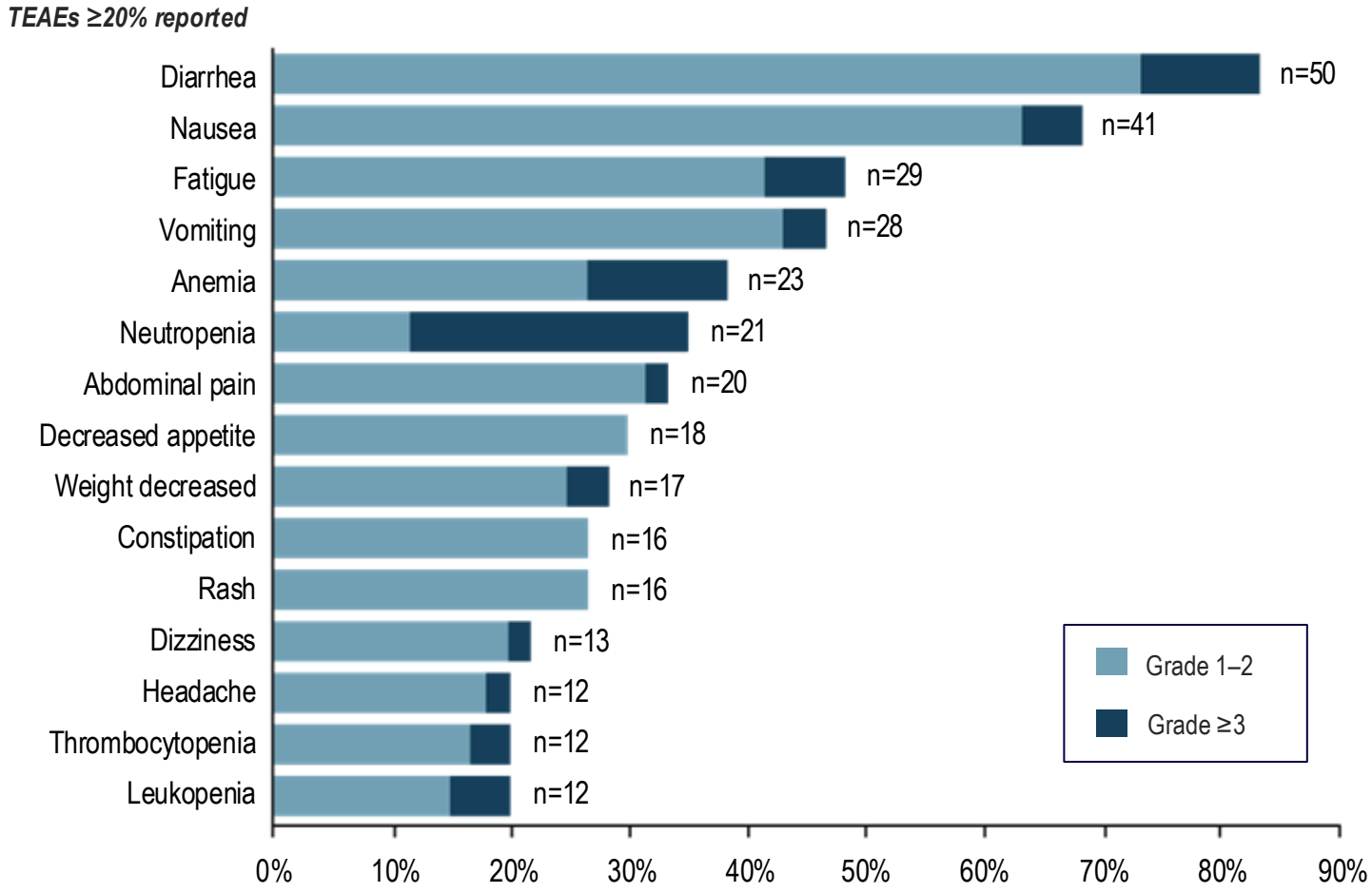
ELEVATE: Phase 2 trial of elacestrant + abemaciclib adverse events[1]

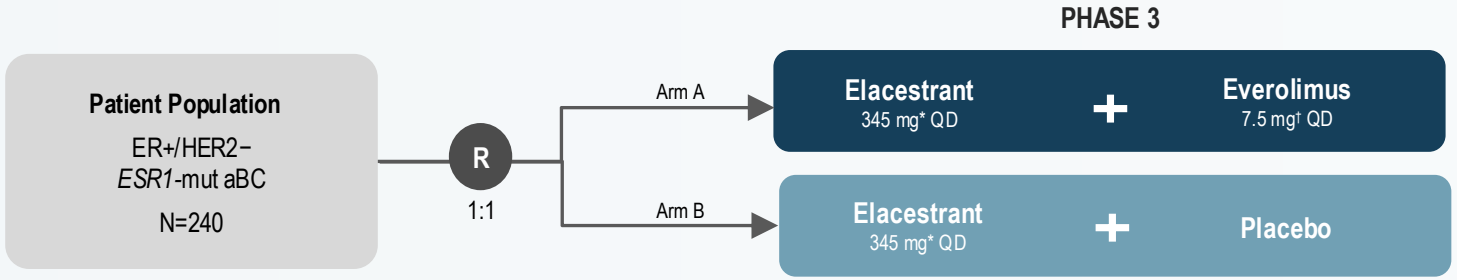


- The safety profile is consistent with either abemaciclib plus standard ET or elacestrant
- No bradycardia or photopsia were reported, and no new safety signals were observed
- Any TEAE leading to elacestrant + abemaciclib drug withdrawal 0%
- Any TEAE leading to elacestrant + abemaciclib drug reduction 5%

Data cut-off: Sept 15, 2025. TEAEs, Treatment-emergent adverse events.

1. Open-Label Umbrella Trial to Evaluate Safety and Efficacy of Elacestrant in Various Combination in Patients With Metastatic Breast Cancer (ELEVATE). ClinicalTrials.gov. May 20, 2024. Accessed August 26, 2024. https://clinicaltrials.gov/trial/NCT05563220.

Ongoing oral SERD combination studies
ADELA: Phase 3 trial of elacestrant + everolimus vs elacestrant + placebo[1,2]



PHASE 3 OBJECTIVES

Primary: Evaluate PFS based on BIRC‡

Key Secondary: Evaluate OS determined locally by investigator

Secondary: Evaluate investigator-assessed PFS, BIRC and investigator-assessed ORR, CBR, DoR, TTR, and best percentage of change in tumor burden,§ safety, and HRQoL

STRATIFICATION FACTORS

- Presence of visceral metastases (yes vs no)
- Duration of prior CDK4/6i therapy (≥12 mo vs <12 mo) in the advanced setting

KEY INCLUSION CRITERIA

- Women (pre-‖, peri-‖, or postmenopausal) and men age ≥18 years
- Histologically or cytologically confirmed ER+/HER2− unresectable locally recurrent or metastatic disease
- Confirmed *ESR1*-mutation
- PD on prior ET + CDK4/6i for aBC after ≥6 mo
  - Patients receiving CDK4/6i-based therapy in the adjuvant setting are eligible if PD is confirmed after ≥12 mo of treatment but no more than 12 mo following CDK4/6i treatment completion
- No prior chemotherapy in the advanced setting
- Previously received 1–2 lines of ET for aBC
  - Progression during or within 12 months of adjuvant ET is considered as a line of ET for advanced disease
- No prior elacestrant or other investigational SERDs¶, PROTAC, CERAN, or novel SERM, and/or PI3K/AKT/mTOR inhibitors, including everolimus
- ECOG PS 0 or 1
- Adequate hematologic and organ function

KEY EXCLUSION CRITERIA

- Formal contraindication to ET defined as visceral crisis and/or rapidly or symptomatic progressive visceral disease
- Received treatment with approved or investigational cancer therapy ≤14 days prior to randomization (except for fulvestrant that must be administered ≥28 days before randomization)
- Known active uncontrolled or symptomatic CNS metastases, metastasis-related spinal cord compression, and/or leptomeningeal disease
- Concurrent malignancy or malignancy within 3 years before randomization

*Elacestrant 345 mg is equivalent to 400 mg elacestrant hydrochloride. †Everolimus dose per RP2D from ELEVATE (NCT05563220) trial. ‡Through the use of RECIST v.1.1. §Based on a BIRC and local investigator assessment through the use of RECIST v.1.1. ‖Receiving a LHRH analogue for ≥28 days prior to study randomization and are planning to continue LHRH agonist treatment during the study. ¶Fulvestrant is permitted if treatment was administered ≥28 days before randomization.

a/mBC, advanced or metastatic breast cancer; AKT, protein kinase B; BIRC, blinded independent review committee; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CERAN, complete estrogen receptor antagonist; CNS, central nervous system; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; ER, estrogen receptor; ESR1, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRQoL, health-related quality of life; LHRH, luteinizing hormone-releasing hormone; mBC, metastatic breast cancer; mo, months; mTOR, mammalian target of rapamycin; mut, mutated; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI3K, phosphatidylinositol-3 kinase; PROTAC, proteolysis targeting chimera; QD, once daily; R, randomization; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; TTR, time to response.

References: 1. Elacestrant + Everolimus in Patients ER+/HER2-, ESR1mut, Advanced Breast Cancer Progressing to ET and CDK4/6i. (ADELA). ClinicalTrials.gov. April 26, 2024. Accessed July 29, 2025. https://clinicaltrials.gov/study/NCT06382948; 2. A randomized phase 3, double-blind, placebo-controlled study of elacestrant plus everolimus or placebo in patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative, ESR1-mutated, advanced breast cancer progressing to endocrine therapy and CDK4/6 inhibitors. MEDOPP545. December 20, 2023 (EUCT number: 2024-512926-27-00).Clinical trial collaboration with MEDSIR.

Key takeaways

Second-line treatment choices are defined by the **eligibility to receive endocrine therapy** and are driven by **biomarker status**. For patients whose tumors retained endocrine-sensitivity, **guidelines recommend exhausting sequential ET-based regimens**[1]

EMERALD study patient population reflects real-world practice with 100% prior CDK4/6i, 70% visceral metastases; prior fulvestrant, ChT, and primary endocrine resistance allowed, leading to elacestrant approval in patients with *ESR1*-mut tumors[2]

RWE of elacestrant data shows consistent benefit of ~8–11 months of TTNT in line with the 8.6 months of mPFS in patients with longer prior ET + CDK4/6i exposure (EMERALD study subgroup analysis)[3,4]

In tumors retaining endocrine-sensitivity and coexisting *PIK3CA* and *ESR1* mutations, **elacestrant monotherapy** can be a good option before PI3K/AKTi combination regimens as **data shows similar efficacy with a manageable safety profile**[5]

Oral SERDs show benefit when combined with CDK4/6i or everolimus. The baseline characteristics of these studies are different and should be taken into account when evaluating outcomes[6–8]

AKT, protein kinase B; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; ITT, intention-to-treat; mPFS, median progression-free survival; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RWE, real-world evidence; SERD, selective estrogen receptor degrader; TTNT, time to next treatment.

1. Gennari A, et al. *Ann Oncol*. 2021;32: 1475-1495 2. Bidard FC, et al. *J Clin Oncol*. 2022;40(28):3246–3256; 3.Loyd M, et al. *Clin Cancer Res* 2026; https://doi.org/10.1158/1078-0432.CCR-25-3033;
4. Rugo HS, et al. *Clin Cancer Res* 2026; https://doi.org/10.1158/1078-0432.CCR-25-3040; 5.Rozenblit M, et al. *Breast Cancer Res*. 2021;23(1):14; 6. Rugo HS, et al. ASCO 2025. Abstract 1070; 7. Rugo HS, et al. SABCS 2024. Abstract PS7-07; 8.Jhaveri KL, et al. *N Engl J Med*. 2025;392(12):1189–1202.

Biomarker driven treatment decisions: Evolution of *ESR1* testing

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Why to test for biomarkers:
The clinical utility of testing mutations drives therapeutic decisions in mBC

Actionable information

Mutation testing provides clinically actionable information that directly influences treatment selection and sequencing decisions[1,2]

Intrinsic mutations

Identification of *PI3K*/*AKT*/*PTEN* alterations enable precision therapy for PI3K or AKT inhibitors, demonstrating reduction in the risk of progression or death[3-7]

ESR1 acquired mutations

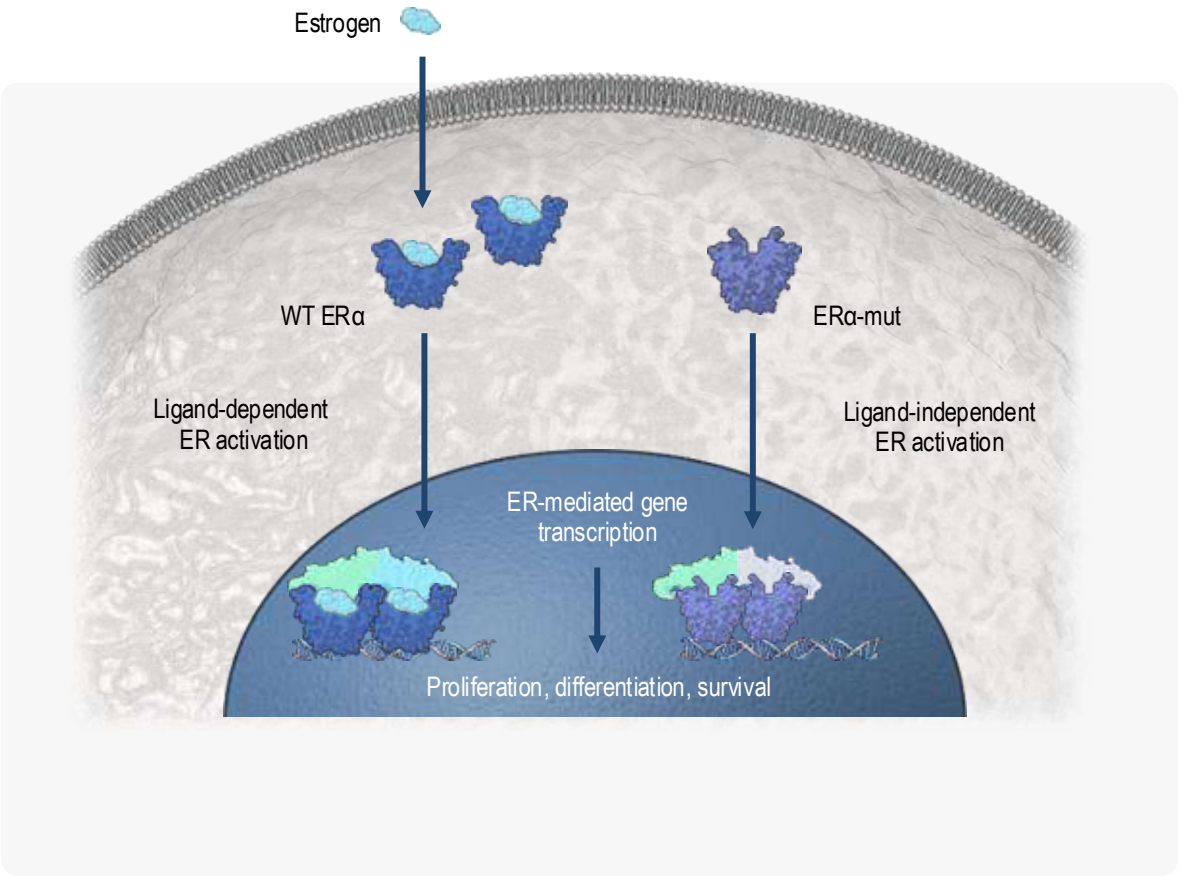
ESR1 mutations guide clinicians toward more effective treatment approaches, as tumors become resistant to SOC endocrine therapy, even in the context of coexisting intrinsic mutations[8-10]

AKT, protein kinase B; ESR1, estrogen receptor 1 gene; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; SOC, standard of care.

1. Burstein HJ, et al. J Clin Oncol. 2023;41(18):3423-3425; 2. Liao H, et al. Front Oncol. 2020;10:587671; 3. André F, et al. N Engl J Med. 2019;380(20):1929–1940; 4. Chia S, et al. ASCO 2023. Abstract P1078; 5. Turner S, et al. SABCS 2021. PD15-01; 6. Turner NC, et al. *N Engl J Med*. 2023;388(22):2058–2070; 7. Oliveira M, et al. *Ann Oncol*. 2023;8(1 suppl 4):101376 Poster 187O; 8. Bardia A, et al. *Clin Cancer Res*. 2024;30(19):4299–4309; 9. Bardia A, et al. SABCS 2022. Abstract GS3–01; 10. Bardia A, et al. SABCS 2024. P1-01-25.

Why to test for *ESR1*-mut:
ESR1-mut are a mechanism of acquired endocrine resistance

- *ESR1*-mut are:[1–8]
  - Acquired under the selective pressure of ET, particularly AI, and are rarely detected in the primary tumor
  - Subclonal and heterogeneous within the tumor
  - Commonly affecting the ligand-binding domain of ERα, resulting in ligand-independent ERα activation and constitutive signaling.
  - One of the main mechanisms of acquired endocrine resistance and a key driver of disease progression



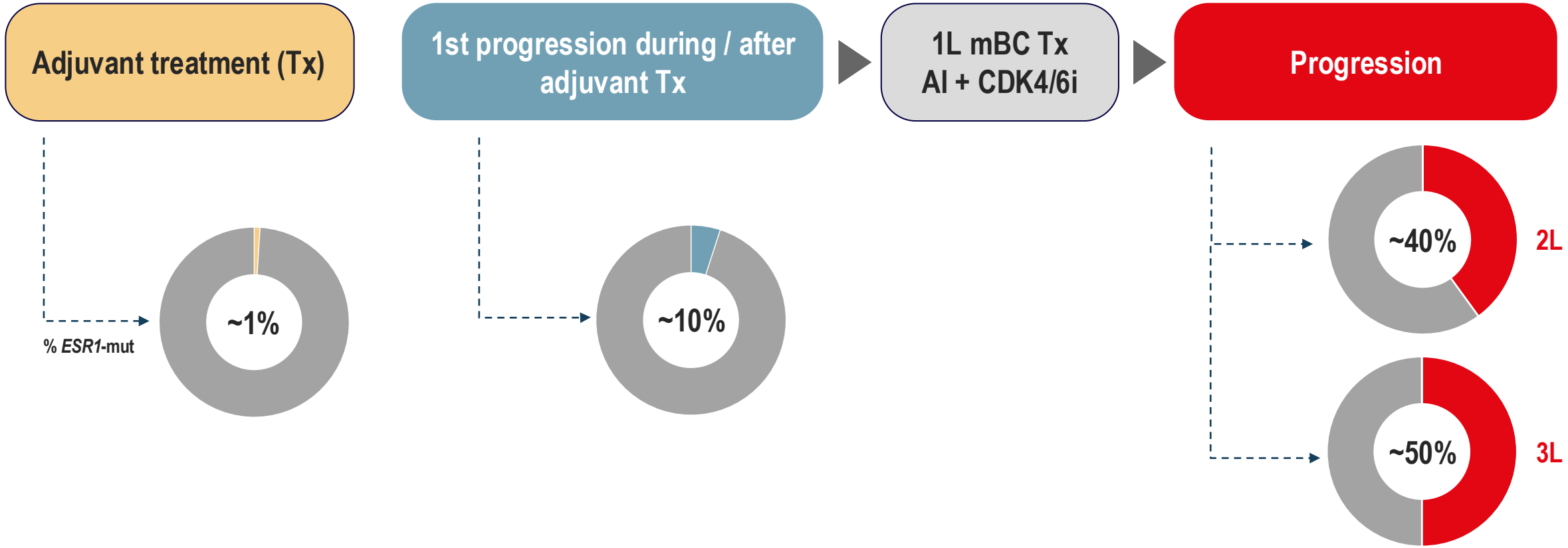
AI, aromatase inhibitors; BRCA, breast cancer gene; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; mut, mutation/mutated; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; wt , wild type.

1. Clatot F, et al. *Breast Cancer Res*. 2020;22(1):56; 2. Chandarlapaty S, et al. *JAMA Oncol*. 2016;2(10):1310-1315; 3. Turner NC, et al. *Clin Cancer Res*. 2020;26(19):5172-5177;
4. Zundelevich A, et al. *Breast Cancer Res*. 2020;22(1):16;5. Schiavon G, et al. *Sci Transl Med*. 2015;7(313):313ra182; 6. Tarabichi M, et al. *Nat Methods*. 2021;18(2):144-155; 7. Dustin D, et al. *Cancer*. 2019;125(21):3714-3728;
8. Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85.

When to test for *ESR1*-mut: Longer exposure to ET in mBC increases *ESR1*-mut prevalence[1–10]

Early breast cancer[1–3,5,7]

Advanced / metastatic breast cancer[2–14]



1/2/3L, first/second/third line; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ESR1, estrogen receptor 1 gene; ET, endocrine therapy; mBC, metastatic breast cancer; mut, mutation; Tx, treatment.

1. Jeselsohn R, et al. *Clin Cancer Res*. 2014;20(7):1757–1767; 2. Allouchery V, et al. *Breast Cancer Res*. 2018;20(1):40; 3. Schiavon G, et al. *Sci Transl Med*. 2015;7(313):313ra182; 4. Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85; 5. Toy W, et al. *Nat Genet*. 2013;45(12):1439–1445; 6. Bidard FC, et al. *J Clin Oncol*. 2022;40(28):3246–3256; 7. Jhaveri K, et al. *Ann Oncol*. 2023;34(suppl 2):S334–S390; 8. Lin N, et al. *Ann Oncol*. 2023;34(suppl 2):S334–S390; 9. Bhave MA, et al. *Breast Cancer Res Treat*. 2024; 2024;207(3):599–609. 10. Lee N, et al. *Int J Mol Sci*. 2020;21(22):8807; 11. Kalinsky K, et al. *J Clin Oncol*. 2024;42(17 suppl): Abstract LBA1001; 12. Jhaveri KL, et al. *N Engl J Med*. 2025;392(12):1189–1202; 13. Miguel M, et al. *J Clin Oncol*. 2024;42(18):2149–2160; 14. Tolaney SM, et al. *J Clin Oncol*. 2023;41(24):4014–4024.

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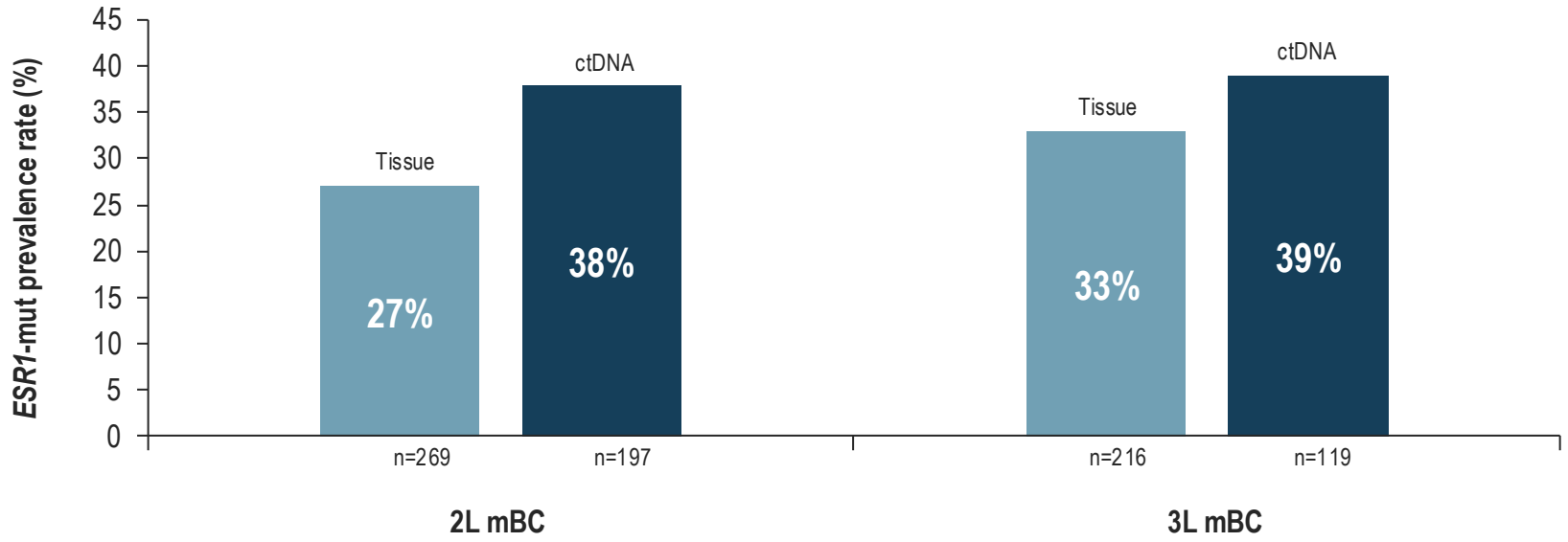
How to test for *ESR1*-mut: ctDNA is the preferred testing methodology due to greater sensitivity.

ESR1-mut are subclonal and heterogeneous within the tumor; therefore, all mutations may not be detected in a tissue biopsy[1–3]

ESR1*-mut prevalence rate by line of therapy in tissue and liquid biopsy[4]



ctDNA TF ≥1% showed a markedly higher prevalence in 2L (57%, n=104) and 3L (59%, n=61) of any of the genomic alterations assessed[4]

*Included patients with HR+/HER2− mBC who underwent genomic testing using tissue or liquid comprehensive profiling (GCP) assays at Foundation Medicine during routine care.

2L, second line; 3L, third line; ctDNA, circulating tumor DNA; *ESR1*, estrogen receptor 1; HER2=human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; mut, mutation/mutated; TF, tumor fraction.

1. Tarabichi M, et al. *Nat Methods*. 2021;18(2):144-155; 2. Dustin D, et al. *Cancer*. 2019;125(21):3714-3728; 3. Burstein HJ, et al. *J Clin Oncol*. 2023;41(18):3423–3425; 4. Bhave MA, et al. *Breast Cancer Res Treat*. 2024.

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How to test for *ESR1*-mut: Tissue vs liquid biopsy

Tissue biopsy[1–5]

- Low sensitivity for *ESR1*-mut
- Invasive
- Long turnaround time
- Given the subclonal and heterogeneous nature of *ESR1*-mut within the tumor, all mutations may not be detected
- Primary archival tissue should not be used, as *ESR1*-mut are typically acquired during the metastatic breast cancer treatment

Liquid biopsy[1–3,6–8]

- High sensitivity for *ESR1*-mut
- Minimally invasive
- Fast sample acquisition
- Reveals tumor heterogeneity, including presence of subclonal *ESR1*-mut from all metastatic disease sites

Available *ESR1*-mut detection methods include[9,a]**:**

- NGS (may be part of a solid tumor panel)
- Digital PCR assays

[a]Physicians should use discretion to determine the appropriate test. Refer to diagnostic manufacturers' technical information to ensure ESR1 gene coverage.

ESR1, estrogen receptor 1 gene; mut, mutation; NGS, next-generation sequencing; PCR, polymerase chain reaction.

1. Lone SN, et al. *Mol Cancer*. 2022;21(1):79; 2. Pascual J, et al. *Ann Oncol*. 2022;33(8):750–768; 3. Spoerke JM, et al. *Nat Commun*. 2016;7:11579; 4. Franken A, et al. J Mol Diagn. 2020;22(1):111–121; 5. Gradishar WJ, et al. *J Natl Compr Canc Netw*. 2023;21(6):594–608; 6. Tarabichi M, et al. *Nat Methods*. 2021;18(2):144–155; 7. Dustin D, et al. *Cancer*. 2019;125(21):3714–3728; 8. Burstein HJ, et al. *J Clin Oncol*. 2023;41(18):3423–3425; 9. Lee N, et al. *Int J Mol Sci*. 2020;21(22):8807.

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Guidelines indicate the importance of *ESR1*-mut testing

Patients should get tested for *ESR1*-mut at each progression on their metastatic treatment, if not detected previously[1–6]

ESMO

European Society of Medical Oncology (ESMO)[1–3]

- *ESR1*-mut should **preferentially be tested in ctDNA**
- **After 1L progression *ESR1*-mut should be tested** and at each subsequent progression if not detected previously

NCCN

National Comprehensive Cancer Network® (NCCN®)[4,5]

- **Detection of *ESR1*-mut:** Blood-based ctDNA is preferred. Methodology could be NGS or PCR
- Given the acquired nature of *ESR1*-mut during metastatic breast cancer treatment, **primary archived breast cancer tissue should NOT be used** as a source of tumor tissue for *ESR1*-mut testing

ASCO

American Society of Clinical Oncology (ASCO)[6]

- **Detection of *ESR1*-mut:** Blood-based ctDNA is preferred owing to greater sensitivity
- *ESR1*-mut develop in response to selection pressure during ET and are typically undetectable in the primary tumor
- Patients whose tumor or ctDNA tests remain *ESR1*-wt may warrant re-testing at subsequent progression(s) to determine if an *ESR1*-mut has arisen

ctDNA, circulating tumor DNA; ESR1, estrogen receptor 1; ET, endocrine therapy; mut, mutation; NGS, next-generation sequencing; PCR, polymerase chain reaction; wt, wild-type.

References: 1. Mosele MF, et al. *Ann Oncol*. 2024;35(7):588–606; 2. Pascual J, et al. *Ann Oncol*. 2022;33(8):750–768; 3. Gennari A, et al. *Ann Oncol*. 2021;32(12):1475–1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.2 April 2025 (Accessed July 2025); 4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.4.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed October 15, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way; 5. Gradishar WJ, et al. *J Natl Compr Canc Netw.* 2023;21(6):594–608; 6. Burstein HJ, et al. *J Clin Oncol*. 2023;41(18):3423–3425.

Key takeaways

Second-line treatment choices are defined by the **eligibility to receive endocrine therapy** and are driven by **biomarker status**[1]

About 50% of *ESR1*-mut are found at progression on prior ET in the metastatic setting[2–6]

***ESR1*-mut testing should occur at each progression on ET** if not detected previously, due to increasing chances of finding it[7–10]

Because *ESR1*-mut are subclonal and heterogeneous, they are not always detected with tissue biopsy. Blood-based ctDNA is considered the preferred testing methodology for *ESR1*-mut[10–12]

Archival tissue from primary tumor should NOT be used to identify *ESR1*-mut, as *ESR1*-mut develop mainly during metastatic treatment[12]

1L, first line; BRCA, BReast CAncer gene; ctDNA, circulating tumor DNA; ESR1, estrogen receptor 1; ET, endocrine therapy; OS, overall survival; PFS2, time from randomization until progression on subsequent therapy; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. Gennari A, et al. *Ann Oncol*. 2021;32(12):1475–1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.2 April 2025 (Accessed July 2025); 2. Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85; 3. Bidard FC, et al. *Lancet Oncol*. 2022;23(11):1367–1377; 4. Santiago Novello RG, et al. *ESMO Open*. 2023;8(suppl 4):104409. Abstract 220P; 5. Lin JL, et al. *Ann Oncol*. 2023;34(suppl 2):S334–S390; 6. Bhave MA, et al. *Breast Cancer Res Treat*. 2024;207(3):599–609; 7. Jeselsohn R, et al. *Clin Cancer Res*. 2014;20(7):1757–1767; 8. Jeselsohn R, et al. *Cancer Cell*. 2018;33(2):173–186; 9. Allouchery V, et al. *Breast Cancer Res*. 2018;20(1):40; 10. Burstein HJ, et al. *J Clin Oncol*. 2023;41(18):3423–3425; 11. Turner NC, et al. *Lancet Oncol*. 2020;21(10):1296–1308; 12. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.4.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed October 6, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org.

Q&A / Discussion

Faculty